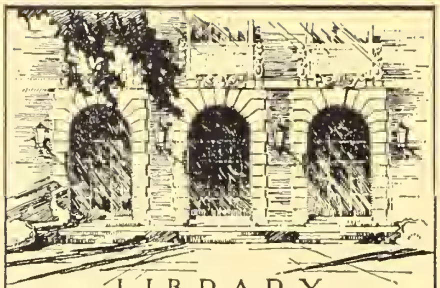

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ORGANIC SEMINAR ABSTRACTS

1967-68

Semester I

Department of Chemistry and Chemical Engineering

University of Illinois

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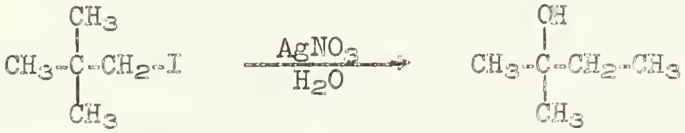
THE NEOPENTYL CATION REARRANGEMENT

Reported by David A. Simpson September 18, 1967

INTRODUCTION

Reactions of neopentyl derivatives under carbonium ion conditions are known to proceed with rearrangement to give substitution and elimination products derived from the t-amyl cation. For example, treatment of neopentyl iodide (1) with aqueous silver nitrate yields t-amyl alcohol (2), obviously the product of a rearrangement.[1]



$$CH_3\text{-}C(CH_3)_2\text{-}CH_2\text{-}I \xrightarrow[H_2O]{AgNO_3} CH_3\text{-}C(OH)(CH_3)\text{-}CH_2\text{-}CH_3$$

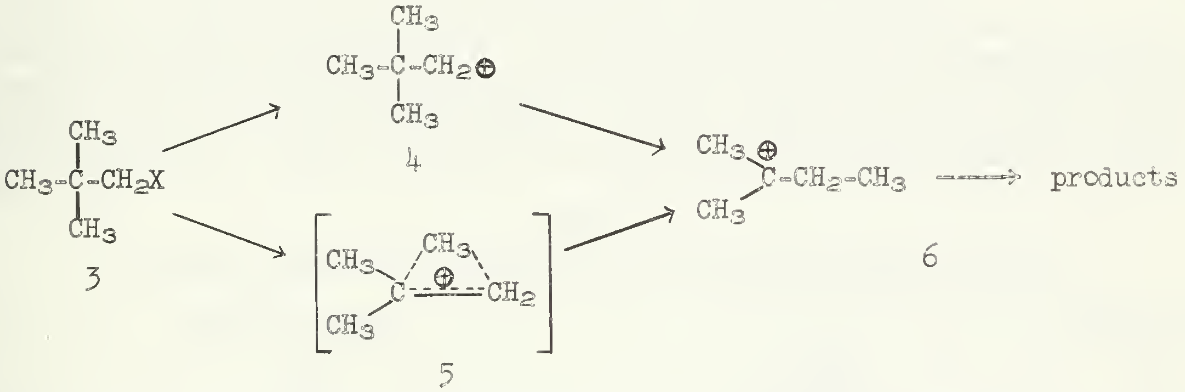
1 2

This reaction has long been considered an example of a general class of rearrangement reactions which includes the camphene hydrochloride rearrangement and the pinacol rearrangement.[2] These changes are classical examples of the Wagner-Meerwein rearrangement.

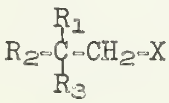
In 1942 Skell and Hauser questioned the timing of this rearrangement. It was proposed that the neopentyl cation may never be formed, but may give the more stable t-amyl cation directly. Thus the removal of the leaving group and the shift of the electron pair with its methyl group would occur simultaneously. The authors suggested that this hypothesis would account for the apparent absence of unrearranged products.[3]

Since that time, there has been a continuing controversy over the mechanism of the neopentyl cation rearrangement. The problem is illustrated in Scheme I. In its simplest form the question is whether the rearrangement involves two steps or simply one. That is, in the conversion of neopentyl derivatives (3) to products, do the ionization and rearrangement steps take place separately (3→4→6) with the involvement of the classical neopentyl cation (4) as a discrete intermediate; or are they concerted (3→5→6) with ionization to give a bridged cation? In either case there remains a question of whether the structure in which the migrating group forms a bridge is a relatively stable intermediate which leads to product(s) directly by reaction with nucleophile or simply a transient on the way to a new (rearranged) classical cation.[4,5]

Scheme I



The body of the abstract is divided into two parts: I, evidence for a concerted mechanism; and II, evidence for a two-step mechanism. Where appropriate, the nature of the bridged structure will be discussed under each section. This seminar will consider neopentyl derivatives of the following general formula: where R_1, R_2, and R_3 may not be a phenyl ring; R_1R_2 may not be incorporated into a cyclopropyl ring; but R_1, R_2 and R_3 may be part of a bicyclic system. Only liquid phase rearrangements will be investigated.

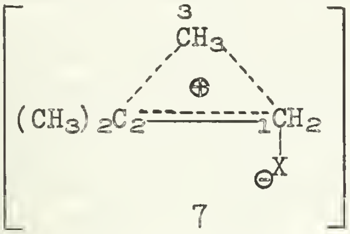


$$R_2\text{-}C(R_1)(R_3)\text{-}CH_2\text{-}X$$

X = $-OTs$, $-OBs$, $-NH_2$, $-Cl$, $-Br$, $-I$ and $-OH$

EVIDENCE FOR A CONCERTED MECHANISM

A concerted rearrangement implies that the 1,3-bond begins to form before the leaving group has receded to its transition state distance (7). If this occurs the migration of the methyl group will assist the expulsion of the leaving group.[6] The neighboring methyl group thus assumes the role of the nucleophilic solvent molecule at the rear, and the transition state has a bridged-ion structure (7). Therefore a rate enhancement could result if the first intermediate were the t-amyl cation (6) or the bridged ion (5).[1] The test is thus kinetic. Indeed much of the evidence in favor of the concerted mechanism is based on observations of rate enhancement in neopentyl systems.



7

Winstein and Marshall measured the solvolysis rates for a series of primary p-toluenesulfonates in formic acid at 75°, the observed relative rates are reported in Table I. The fact that the formolysis of neopentyl tosylate, with its very large steric hindrance to back-side solvent attack, is just as rapid as that of ethyl tosylate was interpreted as a rate enhancement ascribed to rearrangement.[7] This conclusion assumes that the formolysis of the ethyl derivative is far from "limiting", and that its rate is higher than it would be were it limiting. Evidence that solvolysis of ethyl p-toluenesulfonate is not close to "limiting" in type has recently been reported by Lee and Frost.[8]

Table I

Rate Comparsions for Solvolysis of ROTs in HCOOH at 75°

R	Relative Rate	R	Relative Rate
Me	0.56	i-Bu	1.22
Et	1.0	neoPen	1.0

McElrath and co-workers have studied the acetolysis of several alkyl-substituted neopentyl-p-bromobenzenesulfonates. Investigation of such a series should give information concerning the participation of R and CH_3 in the rate-controlling ionization, and the possible appearance of steric acceleration resulting from the relief of B-strain. Table II shows rate enhancements observed relative to the CH_3 member.

Table II

Relative Rates of Acetolysis of $RC(CH_3)_2-CH_2-OBs$ at 59.7°

R	Relative Rate	R	Relative Rate
CH_3	1.0	$i-C_4H_9$	4.1
C_2H_5	2.4	$i-C_3H_7$	7.1
$n-C_3H_7$	2.3	$sec-C_4H_9$	7.9
$n-C_4H_9$	2.4	$t-C_4H_9$	34.0

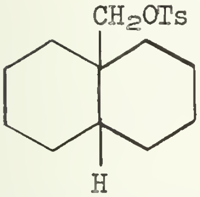
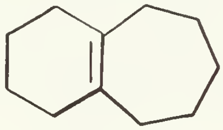
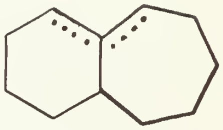
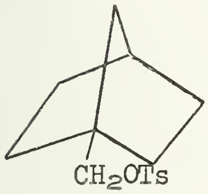
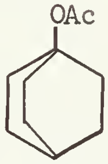
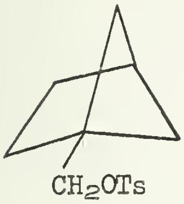
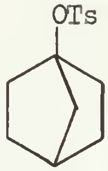
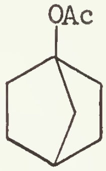
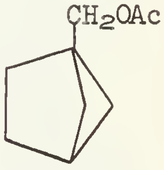
The authors noted the following trends: (1) lengthening the chain in R without branching beyond C_γ ($R=C_2H_5, n-C_3H_7$, and $n-C_4H_9$) gave a constant relative rate of 2.4; (2) the effect of substitution of one, two, and three alkyl groups on C_γ ($R=C_2H_5, i-C_3H_7$, and $sec-C_4H_9$, $t-C_4H_9$) resulted in relative rates of 2.4, 7-8, and 34, respectively; (3) branching of the R chain at C_δ ($R=i-C_4H_9$) gave a relative rate of 4.1.[9] This overall variation of rate with structure corresponds closely to that observed for the structurally similar tertiary chlorides investigated by Brown and co-workers. Here the rate increases were interpreted as resulting from a release of steric strain.[10] Unlike the series of tertiary chlorides, all the brosylates gave completely rearranged products. As a result of the above trends and the fact that estimated steric strain in branched hydrocarbons corresponding to $RC(CH_3)_2CH_2OBs$ parallel the observed increases in reaction rate, the authors explain the rate variations by a combination of carbon participation and release of B-strain.[9] However, the relative contributions of carbon participation and B-strain to the rate increases could not be assessed. In fact, the effects may merge in the reacting molecule and

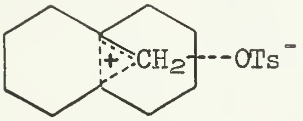
perhaps participation is a means of relief of steric strain.[11]

Some information concerning the effect of strain on anchimeric assistance may be had by measuring solvolysis rates of cyclic and bicyclic primary neopentyl-type arenesulfonates. Here the migrating group is an integral part of a fused ring system. The compounds to be discussed along with relevant data are found in Table III.

Dauben and Rogan studied the acetolysis of cis- and trans-9-decalylcarbinyl p-toluenesulfonates (8).[12] It was found that the rate of each isomer was the same, being more rapid than that of neopentyl tosylate by a factor of about five. The products are olefins of the 5,4,0-undecene series showing that the 1,9-bond of the decalin system has migrated. The authors ascribed the enhanced rate of reaction to anchimeric assistance and thus to the involvement of a bridged-ion transition state. Of the two possible bridged-ions, (11) and (12), transition structure (12) was favored by the authors since it is relatively free from strain and in addition could relieve the conformational strain present in the starting materials. Transition state (11) would be highly strained since it requires a partial double bond at the bridge head. The authors attribute the enhanced rate to the relief of conformational strain.[12]

Table III

Compound		Relative Rate (Neopentyl=1)	Products and Yield
 cis or trans	8	~5	 cis: 74% trans: 80%  26% 20%
	9	~7-8	 85%
	10	194	 90%  8%  ~2%



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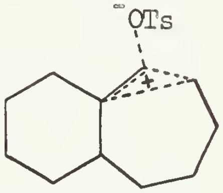
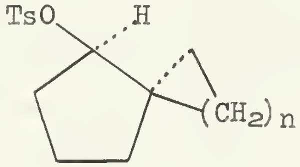


12

The acetolysis of bicyclo [2.2.1] heptane-1-methyl tosylate (9) was studied independently by Bixler and Niemann, and Wiberg and Lowry. Bixler and Niemann suggested that the rate enhancement observed could be due to anchimeric assistance, for participation would involve rearrangement to a bicyclo [2.2.2] octyl system with relief of some steric strain.[13] Wiberg and Lowry also found that the reaction was about eight times faster than neopentyl tosylate. The only product that could be

isolated was 1-bicyclo [2.2.2] octyl acetate. A comparison of the rates of acetolysis of bicyclo [2.2.1] heptane-1-methyl tosylate (9) with bicyclo [2.1.1] hexane-1-methyl tosylate (10) proved interesting. With the bicyclo [2.1.1] hexane derivative, the driving force from relief of strain would be greater, but the resulting carbonium ion, the 1-bicyclo [2.2.1] heptyl ion is known to be very poor. Thus it was expected that the rearrangement would proceed with difficulty. However, it was found that the rate of reaction of this compound (10) was 24 times as great as that of the bicyclo [2.2.1] heptane derivative (9). The authors suggest that the marked difference between the two ring systems indicates that rearrangement occurs at an earlier stage of carbonium ion formation in the bicyclo [2.1.1] compound. This was considered reasonable in view of the destabilization of the 1-norbornyl cation, and further suggests that the reaction most probably involves an internal rearrangement in which charge separation is minimized.[14]

Krapcho and Benson have studied the acetolysis rates of the spirane tosylate system (13) where n=2,3, and 4, and compared them to the rate of 2,2-dimethylcyclopentyl tosylate (14). The large rate accelerations observed with adjacent cyclobutyl (n=2) and cyclopentyl (n=3) ring systems were assigned to relief of ring strain by anchimeric assistance.[15]



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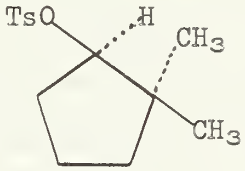


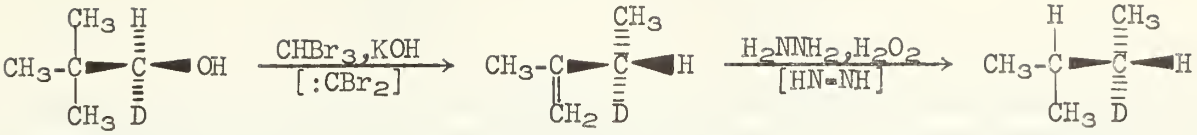
14

The enhanced rates observed for these cyclic and bicyclic systems have been ascribed to relief of steric strain through carbon participation. This then is evidence for a concerted rearrangement embracing a bridged transition state. Criticism concerning the conclusions of the authors is reserved for part II of the abstract.

Saunders and associates have studied the relation between rate and migration aptitude in several neopentyl derivatives in an effort to determine whether the ionization and migration are stepwise or concerted.[16-19] Rates, migration aptitudes, and partial rate factors were determined for solvolysis of a series of 2,2-dimethyl-3-(p-X-phenyl)-1-propyl p-toluenesulfonates (X=CH_3O, CH_3, H, Cl, CF_3). The solvolysis rates varied with the substituent being about four times faster for X=CH_3O than for X=CF_3. Correlation of the rate constants with the Hammett equation gave a ρ value which the authors concluded was larger than that expected for simple ionization without participation. Methyl migrated faster than benzyl in all cases, but the methyl:benzyl migration aptitude varied from 4.6 for X=CF_3 down to 1.4 for X=CH_3O in acetic acid at 109.58°. A greater preference for methyl migration was observed in formic acid.[18] The evidence obtained is consistent with the concerted mechanism, but, as the authors point out, the results do not require the concerted process.

In addition to the kinetic test for a concerted mechanism, there is also the obvious stereochemical criteria. If ionization and migration are synchronous (7) and the migrating methyl group assumes the role of a nucleophile, then inversion should result at the seat of dissociation.[6] However, if ionization occurs to the free (planar at the cationic carbon atom) neopentyl cation, then there should be racemization at C-1. Saunders and Mosher have applied this test to the "deoxideation" of optically active neopentyl-1-d alcohol.[21,22] See Scheme II. Neopentyl-1-d alcohol (15), prepared by the reduction of trimethylacetaldehyde-1-d by actively fermenting yeast, was treated in boiling aqueous potassium hydroxide with bromoform. The reaction gave optically active 2-methyl-1-butene-3-d (16) in 39% yield, along with 2-methyl-2-butene in 17% yield and neopentyl-1-d alcohol with unchanged optical rotation. The 2-methyl-1-butene-3-d (16) was purified and reduced with hydrazine and hydrogen peroxide (diimide reduction) to give 2-methylbutane-3-d (17), $[\alpha]^{17}$ D -0.85 ± 0.03° (neat). In order to determine the absolute configuration and stereochemical purity of the neopentyl-1-d alcohol, the same optically hydrocarbon (20) was made by established steps starting with resolved

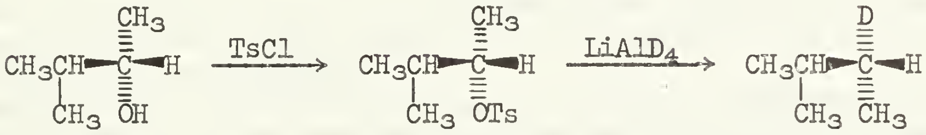
Scheme II



(S)-15 (S)-(+)-16 (S)-(-)-17

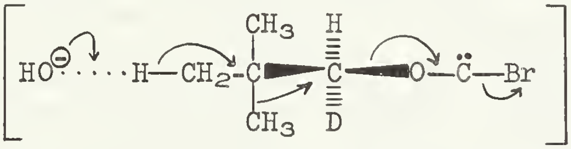
(S)-(+)-3-methyl-2-butanol (18). See Scheme III. Thus the absolute configuration of the 2-methylbutane-3-d (20), $[\alpha]^{20}$ D + 0.76 ± 0.02° (neat), prepared in this

Scheme III

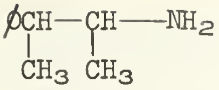


(S)-(+)-18 (S)-(+)-19 (R)-(+)-20

manner is known. On the basis of results in other reported cases the authors claim that there should be no racemization during the synthesis of the tosylate (19), but lithium aluminum deuteride displacements have been accompanied by small amounts of racemization. It was assumed that the product (20) was at least 90% stereochemically pure. Comparison of the product (17) from the "de-oxideation" with the product of known absolute configuration (20) shows that the neopentyl-1-d alcohol possesses the absolute (S) configuration and is nearly stereochemically pure. An nmr study of the esters of the neopentyl-1-d alcohol with (R)-, (S)-, and racemic O-methylmandelyl chloride revealed that it is 99 ± 1% optically pure. Thus the rearrangement was reported to be highly stereoselective. The authors interpreted these results to mean that the rearrangement takes place with inversion at the deuterium-substituted carbon and does not proceed via a free neopentyl cation.[22] However, Karabatsos regards these results as equally compatible with a two step process, provided the methyl migration is faster than or competes favorably with rotation of the -CHD group.[23] Sanderson and Mosher have also considered this question. Thus if the rate of rotation about the C_1-C_2 bond is slow compared to the rate of migration, it is possible for the planar neopentyl cation to be an intermediate and still give a product without complete racemization. Although the authors estimate the energy barrier to rotation to be low and the 2-methyl-1-butene-3-d (16) to be relatively pure stereochemically, they cannot completely discard Karabatsos's mechanism until the stereochemical purity of the 2-methyl-1-butene-3-d can be established.[22] Although the above evidence seems to demand a concerted ionization and migration, a linear concerted pathway involving attack of base on the intermediate neopentoxybromomethylene must be considered.[22]

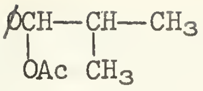


Concerning the concerted process, a very interesting and controversial question presents itself. Could the methyl-bridged transition state (7) lead to a methyl-bridged intermediate, and if so, what is the structure of this intermediate? This question is related to the non-classical carbonium ion controversy, an example of which is the norbornyl cation problem.[25] For a review of some material relevant to this question see footnote 24. The first claim to evidence for a methyl-bridged carbonium ion was presented by Cram and McCarty in an investigation of the deamination of threo- and erythro-3-phenyl-2-butylamine (21).[26] The products of methyl migration (22) were optically active at the migration origin, the benzyl carbon atom having been partially inverted during the methyl migration. Although this result provides some evidence for the intervention of a methyl-bridged carbonium ion intermediate, a second mechanism in which the methyl bridges are transition states rather than discrete intermediates is not excluded by the data.[26]



$\phi CH(CH_3)-CH(CH_3)-NH_2$

21



$\phi CH(OAc)-CH(CH_3)-CH_3$

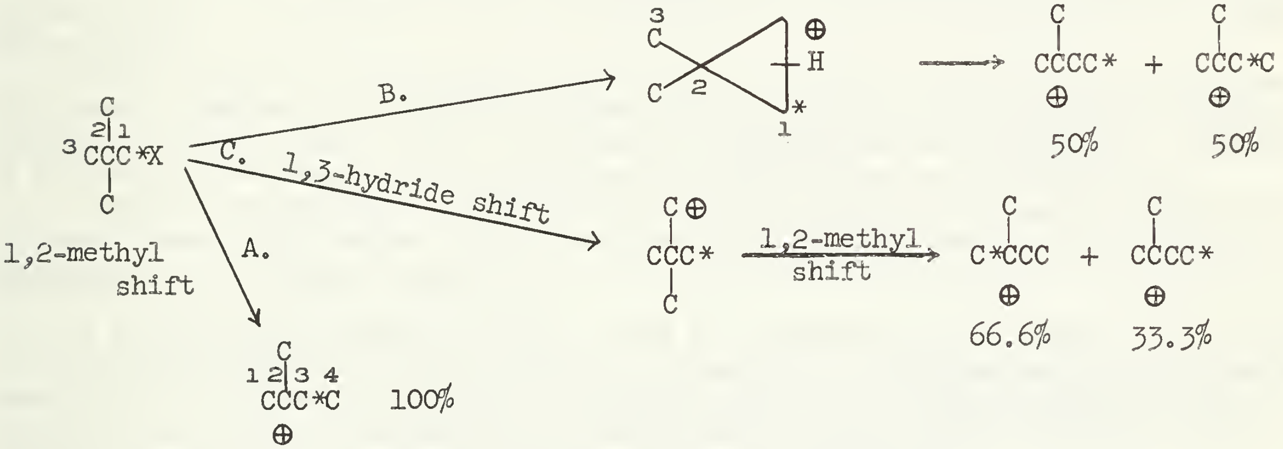
22

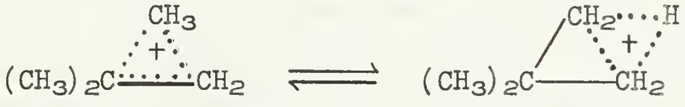
Roberts and Yancey have concluded that a non-classical cation is not an important intermediate in irreversible carbonium ion type reactions of pentamethylethyl derivatives. It is suggested that such methyl-bridged ions are unlikely to be as stable as the equilibrium mixture of classical cations and indeed may only be transition states through which the latter ions are interconverted.[27]

The discovery of cyclopropane formation in certain carbonium ion reactions[28] suggested the possible intermediacy of protonated cyclopropanes. Furthermore, protonated cyclopropanes may be the intermediates which lead to rearranged carbonium ions in Wagner-Meerwein rearrangements.[29] The neopentyl system was chosen for a critical test of this hypothesis.

Karabatsos and associates used nmr and mass spectrometry to analyze the t-amyl alcohols obtained from the deamination of neopentyl-1-^{13}C and neopentyl-1,1-d_2-amines, the solvolysis of neopentyl-1-^{13}C and neopentyl-1,1-d_2 tosylates, and the solvolysis of neopentyl-1-^{13}C iodide. Scheme IV summarizes the isotopic distributions predicted for the various paths on the assumption that isotope effects are negligible and that no further scrambling of atoms occurs once the t-amyl structure is attained. Path A, a 1,2 methyl shift, leads to a t-amyl cation labeled solely at C-3; path B, involving a symmetrically protonated cyclopropane, distributes the label equally between C-3 and C-4; path C, a single 1,3-hydride shift followed by a 1,2-methyl shift, distributes the label between C-1 and C-4 in a 2:1 ratio. Since all the label originally present at C-1 of the neopentyl compounds always ends up at C-3 of the t-amyl alcohol, paths B and C are excluded.[23,30] Skell, Starer and Krapcho have confirmed these results for the de-oxideation of 1,1-dideuterio-neopentyl alcohol.[31] Again only C-3 labeling was present in the products. Thus it would appear the neopentyl cation rearrangement proceeds by a simple 1,2-methyl shift under a variety of conditions of carbonium ion generation. However, although this evidence rules out a symmetrical protonated cyclopropane intermediate, an unsymmetrical edge protonated cyclopropane or a methyl-bridged intermediate (23) are not excluded as possibilities.

Scheme IV



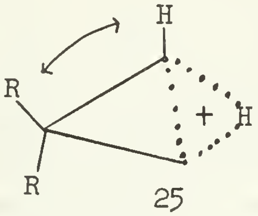


23

24

Edwards and Lesage believe that an edge protonated cyclopropane would give rise to cyclopropane in high yield.[32] Recently Karabatsos has suggested that the methyl-bridged ion might be an intermediate leading solely to the t-amyl cation.[33] Since the deamination of neopentyl amine gives no dimethylcyclopropane,[28] the ideas of Edwards and Karabatsos are compatible if the methyl-bridged ion (23) rearranges to

the very stable t-amyl cation much faster than it equilibrates with 24 or forms 1,1-dimethylcyclopropane.[33] Karabatsos has suggested that a factor which might hinder the equilibration of 23 with 24 is the 1,2-eclipsing interactions (25) in 24.[33] This would help explain why under deamination conditions n-propylamine gives cyclopropane, isobutylamine gives methylcyclopropane to a lesser extent,[29] and neopentylamine gives no dimethylcyclopropane. For the n-propyl case the interactions would be absent (25; R=H) and for isobutylamine one of the R groups would be a methyl and thus some interaction would be present, but not enough to prevent some leakage into the edge protonated form and formation of methylcyclopropane.



25

Equilibrating edge protonated cyclopropanes have been suggested as the best representation of the reactive intermediates involved in the observed isotopic rearrangements in the 1-propanol from the deamination of 1-propylamine.[34] It has also been suggested that methyl-bridged ions may be regarded as transition states in the interconversions between edge-protonated cyclopropanes.[35] Eclipsing interactions in edge protonated cyclopropanes of the neopentyl system may cause a methyl-bridged ion to assume increasing chemical significance. Silver has suggested that the failure to detect 1,1-dimethylcyclopropane in the deamination of neopentyl amine is not a strong argument against the possibility of 23 as an immediate precursor to olefin.[36]

It must be emphasized that arguments supporting the intermediacy of a bridged species in the neopentyl cation rearrangement can only be regarded as evidence for the concerted mechanism in as much as this mechanism would be preferred on the basis of simplicity. A mechanism involving additional steps, that is, formation of the bridged species subsequent to the generation of a discrete neopentyl cation cannot be excluded.

Small amounts of cyclopropane derivatives have been reported in the alumina catalyzed dehydration of several neopentyl-type alcohols. A mechanism involving either a methyl-bridged ion or a protonated cyclopropane was suggested.[37] However, a mechanism involving the concerted loss of H and OH cannot be ruled out.[38]

Thus the evidence for a concerted mechanism appears to be based primarily on observed rate accelerations which have been attributed to anchimeric assistance.

EVIDENCE FOR A TWO-STEP MECHANISM

A two-step rearrangement implies that the leaving group recedes to its transition state distance before formation of the 1-3 bond (7). Thus the migration of the methyl group will not kinetically affect the separation of the leaving group, but the migration must occur soon after ionization since no appreciable quantity of any unrearranged product accompanies the rearranged material.[39]

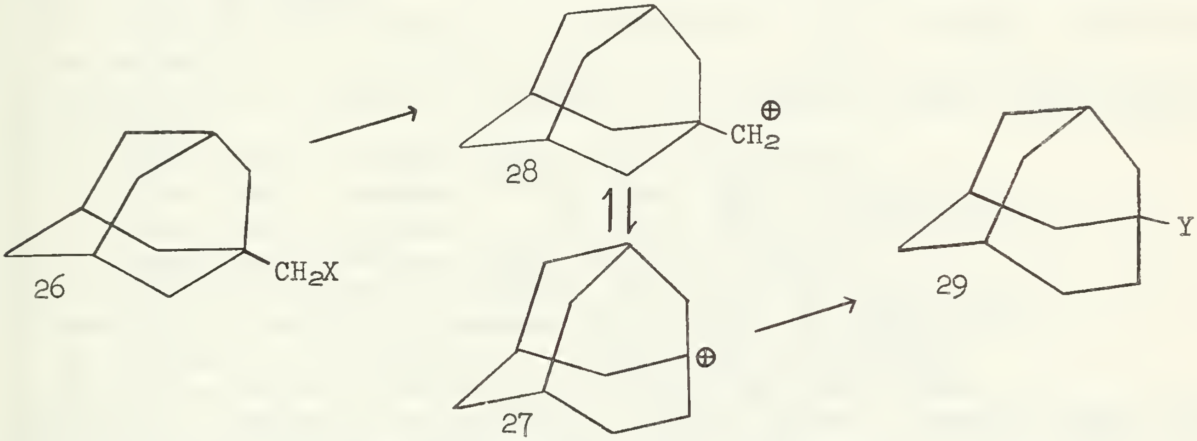
Proponents of the two-step mechanism argue that the enhanced rates in neopentyl solvolyses are too small to be considered strong evidence in favor of participation.[4] For example, neopentyl halides are hydrolyzed (with rearrangement) somewhat more slowly than ethyl halides (without rearrangement),[39,40] whereas 2,2,2-triphenylethyl chloride is hydrolyzed (with rearrangement) over 10,000 times as rapidly. Therefore one could assume the hydrolysis of the neopentyl halides to be virtually unassisted anchimerically.[40]

Nordlander and co-workers have recently argued that the observed rate enhancements are inductive in origin.[4] Streitwieser has found that solvolysis of primary, secondary, and tertiary systems correlate well with Taft's σ^* (inductive) constants.[41] From various reported ρ^* values, Nordlander assumed a $\rho^* = -4.0$ for a limiting ionization mechanism in the primary tosylate series. (This assumption was based on a $\rho^* = -3.5$ reported for the formolysis of several secondary tosylates[42] and the fact that ρ^* for a limiting solvolysis should become more negative from secondary to primary. The ability to predict a value for ρ^* on the basis of empirical considerations may be questioned.) Using this ρ^* it was readily calculated ($\sigma^*_{CH_3} = 0.00$; $\sigma^*_{t\text{-}C_4H_9} = -0.30$)[43] that ethyl tosylate, on a purely inductive basis, should solvolyze some 16-fold more slowly than neopentyl tosylate.[4] The similar rates for these two

tosylates found by Winstein and Marshall may be explained by a competing S_N2 displacement on the less sterically hindered ethyl system.[41]

Thus the small rate enhancements for 8 and 9 recorded in Table III may possibly be explained on a purely inductive basis. Furthermore, some of the enhanced rate observed for 9 and 10 has been attributed to increased ease of direct displacement reactions. Since the $C_\alpha C_\beta C_\gamma$ bond angles in 9 and 10 are constrained to values larger than tetrahedral, it was argued that both compounds, especially 10, may be more susceptible to direct displacement than neopentyl tosylate.[4] However, the absence of significant quantities of unrearranged product (Table III) indicates that any rate enhancement attributable to an S_N2 process must be very small.

Nordlander and associates have recently reported the results of an experiment designed to test the occurrence of participation. Ideally, one needs a neopentyl derivative that would react by an ionic mechanism and still not rearrange. The authors chose 1-adamantylcarbinyl arenesulfonate (26), a molecule with considerable steric bias against rearrangement, as the model compound. Rearrangement of this neopentyl derivative would be much less favorable than the similar transformation 4 → 6 in the parent neopentyl system. The formation of the homoadamantyl ion (27) would be hindered in as much as the strain free quality of the adamantane skeleton would be destroyed. Therefore it was postulated that the solvolysis of neopentyl tosylate and 1-adamantylcarbinyl tosylate should have similar rates if the slow steps involve simple ionization (to 4 and 28, respectively), but that the neopentyl system should solvolyze faster if the rate-determining step involves synchronous ionization and rearrangement.



The acetolysis of 1-adamantylcarbinyl tosylate (26; X=OTs) yielded virtually quantitatively a mixture of 6.8% 1-adamantylcarbinyl acetate (26; X=OAc) and 93.2% 3-homoadamantyl acetate (29; Y=OAc). Neither product was rearranged under the reaction conditions. Unrearranged acetate 26 (X=OAc) arising from an S_N2 process was ruled out since increasing the nucleophilicity of the medium by 5 and 10 equiv of sodium acetate caused no change in the product composition. In all cases the 1-adamantylcarbinyl derivatives solvolyzed slightly faster (not slower) than their neopentyl counterparts (for example: the following relative rates for acetolysis at 75° are reported; neopentyl tosylate, 1.0; 1-adamantylcarbinyl tosylate, 1.7). On the basis of the above arguments the authors favor the two-step mechanism involving initial ionization to the primary cations.[4] It must be emphasized that this argument presupposes that both the neopentyl and adamantyl solvolyses proceed by the same mechanism. It could be argued that the adamantyl system, being a special case, may possibly solvolyze by a different route.

As was previously discussed, the de-oxideation of neopentyl-1-d alcohol has been suggested as evidence for the concerted mechanism. However, the same authors reported that the t-amyl alcohol produced in the silver ion assisted hydrolysis of optically active neopentyl-1-d iodide was optically inactive,[21] a result inconsistent with a concerted rearrangement.

Fraser and Hoffmann have recently reported the formation of unrearranged products and dimethylcyclopropane in the solvolysis of neopentyl tosylate.[44] The neopentyl products were thought to arise from a neopentyl cation, but these products may be formed by an S_N2 process.

In the case of some highly strained cyclic and bicyclic neopentyl systems, the rate studies indicate that participation is not unlikely. In such systems the relief of strain may be coupled with ionization to favor the concerted process. However, in the parent neopentyl system it appears that no definite conclusion is presently possible concerning the timing of ionization and methyl migration.

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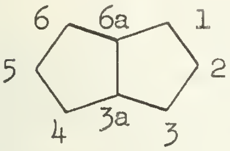
AZAPENTALENES: THE NITROGEN HETEROCYCLIC ANALOGUES OF PENTALENE AND PENTALENE DIANION

Reported by Clayton Mabuni September 25, 1967

The synthesis, structure and chemical properties of the azapentalenes,[1] the nitrogen heterocyclic pentalene analogues, and the azapentalenides, the pentalene dianion analogues are reviewed in this seminar. Because of the emphasis of this discussion, the trivial nomenclature is used, and the pentalene system is numbered as in I. In order to distinguish the pentalene analogues from the pentalene dianion analogues, the former will be referred to as azapentalenes and the latter azapentalenides.



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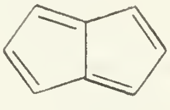
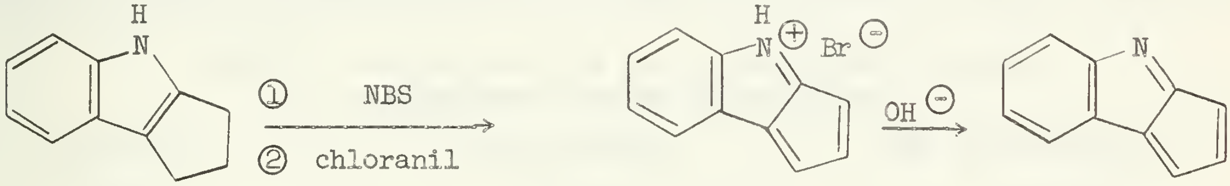


II

The study of the pentalene analogues appears to have arisen directly out of the curiosity generated by the yet unsynthesized, conjugated, nonalternant, 8π-electron, parent pentalene II. Since MO and VB calculations predict large resonance energies (MO: 2.44β,[2] 1.084β[3] and 2.456β;[4] VB: 1.09α,[2] 1.10α[3]) for pentalene, a positive result--the synthesis of an azapentalene--would permit comparison of data such as resonance energies and electronic transition energies to compare with theory. However, the synthesis of the azapentalenes has not appeared to be any easier than the synthesis[5] of the pentalenes.

Paul and Weise in a communication[6] reported the synthesis of the deep violet, azapentalene hydrobromide IV by brominating cyclopenteno-(b)-indole III with N-bromosuccinimide (NBS) and dehydrogenating it with chloranil.

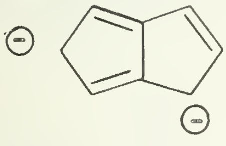


III IV V

The syntheses of two benzoazapentalenes were reported,[7,8] but various attempts to reproduce the work[6,9] and to generate others have proven futile.[9]

The study of the azapentalenides arose from the recognition of the dibenzo-1,3a,4,6a-tetraazapentalenes as a new class of heterocycles. After the structural relationship with pentalene dianion was realized by Carboni, he and others initiated a more systematic investigation of the azapentalenides.

The successful synthesis[5] of the pentalene dianion, but not the parent pentalene seems to be evidence for placing the pentalene system within the set covered by the Huckel Rule. The azapentalenides formed by replacing a methylidene group in pentalene dianion VI by a nitrogen would not appear to have any additional stabilizing influence except, perhaps, for the effects of the heteroatom.



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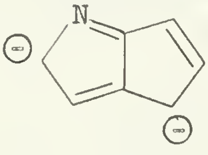
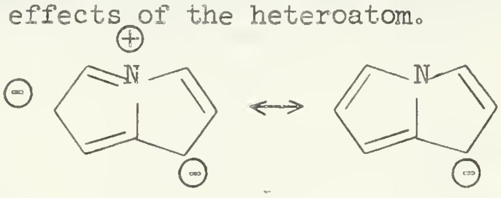


VII

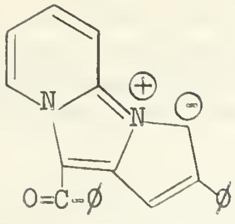


VIII IX

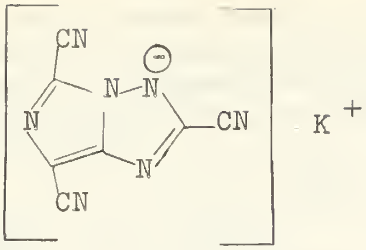
In reducing the amount of charge on the azapentalen~~e~~ide, however, replacement of the bridgehead carbon with nitrogen does appear to provide an additional stabilizing factor. Charge interaction would appear to favor the nitrogen-bridged azapentalenide over either the methylidene-substituted azapentalenide or the pentalene dianion. In the azapentalenides studied, nitrogen occupied at least one bridgehead position.

MONOAZA-BRIDGED PENTALENIDES

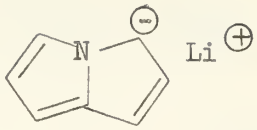
The diazapentalenide structure was proposed for the product X from the condensation reaction of ω-bromoacetophenone and 2-acetaminopyridine by Schilling,[10] et. al. in 1955.



X



XI



XIII

The tetraazapentalenide structure XI was proposed for the $K^{\oplus}$ $C_7N_7^{\ominus}$ product from the reaction of cyanogen and potassium cyanide by Webster[11] in a patent abstract of 1963. The ultraviolet spectrum of the triethylammonium tetraazapentalenide was reported as 314 mμ (ϵ = 16,900), 287 (12,400) and 220 (31,500).

Recently, the parent monoazapentalenide XIII was generated by removing a proton from 3H-pyrrolizine XII with n-butyl lithium by Okamura and Katz.[12] Nmr spectroscopy revealed three different protons with chemical shifts of τ3.71, τ4.01, and τ5.31. Spin-spin decoupling experiments showed $|J_{AB}|$ = 2.1 cps, $|J_{BC}|$ = 3.2 cps and $J_{AC} < 1$ cps. The magnitude of J_{AB} and J_{BC} was interpreted as best representing the proton on C-2 coupling with the adjacent protons on C-1 and C-3. The lowest field absorption was assigned to the C-3 proton, as might be expected for protons on carbons adjacent to a nitrogen in a nitrogen heteroaromatic. Charge densities calculated from nmr chemical shifts are compared with charge densities from HMO calculations (See Table I).

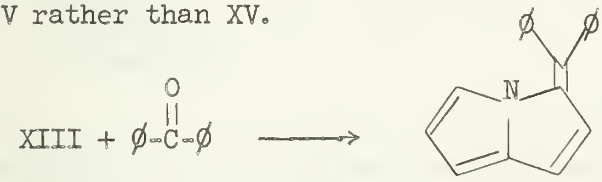
Table I. A Comparison of Charge Densities[a] Obtained from NMR Data and HMO Calculations

Proton at	Charge Density	HMO Charge Density
C-3	- 0.17	- 0.26
C-2	- 0.18	- 0.14
C-1	- 0.32	- 0.30

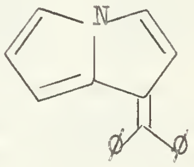
a. W. H. Okamura and T. J. Katz, Tet., 23, 2941 (1967).

Chemically, the most negative carbons appear to be the C-3 and C-5 ones, if the charge distribution of the ground state parallels that of the transition state. Deuteration of lithium azapentalenide (LiAzp) with deuterium oxide showed 4.65% nondeuterated, 83.2% monodeuterated, 10.8% dideuterated and 1.52% trideuterated material by mass spectroscopy of the LiAzp sample that was 11% deuterium oxide.[12] An analysis of the nmr spectra of 3H-pyrrolizine and the deutero-3H-pyrrolizine was cited as evidence consistent with 3-deutero-3H-pyrrolizine.

When LiAzp was reacted with benzophenone, the fulvene type derivative XIV or XV was obtained.[12] The nmr spectrum of the derivative appeared to favor the isomer XIV rather than XV.



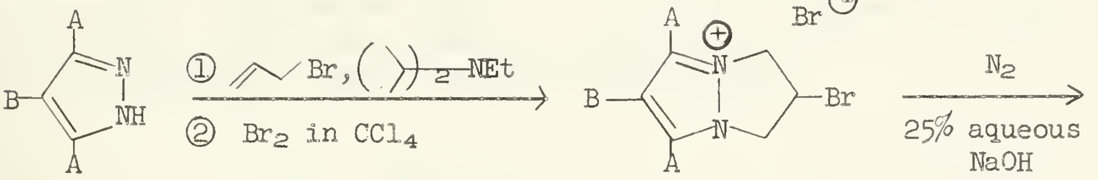
XIV



XV

The basicity of the azapentalenide was indicated by the pKa of 29[12] for XII in comparison to 18.5[13] for indene. XII, whose anion is isoelectronic with napthalene and indene anion, has a large pKa like cycloheptatriene pKa ~36[13]. Indene has a pKa on the order of cyclopentadiene pKa ~15[13], whose anion has substantial electron delocalization energy. Aromatization effects do not appear to play a major role in the stabilization of XIII and, thus, XIII does not appear to be aromatic.

Because both Trofimenko[14,15] and Solomons and Voigt[16] synthesized 3a,6a-diazapentalene (DAP) by essentially the same synthetic sequence, only the former's is given. Trofimenko allylated pyrazole, brominated allyl pyrazole XVIa and dehydrobrominated an aqueous solution of 1,2-(2-bromotrimethylene)-pyrazole XVIIa with sodium hydroxide to obtain DAP[14,15] XVIIIa.



XVIa A=B=H
b A=B=CH_3
c A=CH_3, B=H

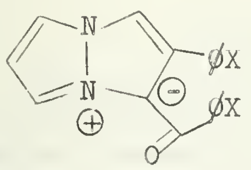
XVIIa A=B=H
b A=B=CH_3
c A=CH_3, B=Br

XVIIIa A=B=H
b A=B=CH_3
c A=CH_3, B=Br

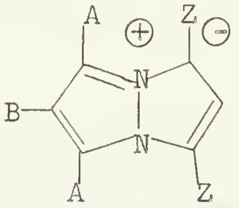
The DAP structure was supported by the molecular ion peak in its mass spectrum at m/e 106 and by its nmr spectrum--doublet at $\tau 2.99$ and a triplet at $\tau 3.35$ with a proton ratio of two to one.[15] (Solomons and Voigt reported a doublet at $\tau 2.95$ and a triplet at $\tau 3.52$ in the ratio two to one in dimethyl sulfoxide-d_6.)[16] The C-1 and C-3 protons were assigned the lower field absorption and the C-2 proton, the higher.

The electronic spectrum of 3a,6a-diazapentalene consisted of an absorption at 284 mμ in deoxygenated ethanol[16] which compared with the 296 mμ band of lithium pentalene dianion in tetrahydrofuran.[17] A comparison of the spectra of pentalene dianion and diazapentalenide with those[18] of the isoelectronic naphthalene and azulene--in 95% ethanol, 312 mμ (log ϵ 2.40), 286 (3.62), 275 (3.75), 266 (3.70) and 221 (4.68); azulene, 700 mμ (log ϵ 2.48), 357 (3.60), 269 (4.67), 236 (4.34) and 193 (4.26)--indicated that the smallest electronic transitions of the former required more energy than those of either naphthalene or azulene.

Bromination and nitration were attempted on the earliest reported diazapentalenides XXa-d. The compound XXa was synthesized by alkylating both nitrogens of pyrazole with ω-bromoacetophenone followed by cyclization and proton abstraction in aqueous sodium bicarbonate.[19] The lack of NH, OH or aliphatic CH stretching absorptions in the infrared and the presence of absorptions only in the region $\tau 2.4$-3.3 in the nmr spectra of the isolated samples, whose elemental analyses were given, were presented as evidence for the diazapentalenide structure. Unlike the simpler diazapentalenides XVIIIa-c, the diazapentalenides XXa-d were water insoluble--being soluble in 6N HCl or concentrated sulfuric acid but not in 0.1N HCl--and were not reported to be air-sensitive. Attempted bromination gave an intractable gum, and nitration was reported to give an unidentified oxidized material.



XXa X=H
b X=p-Cl
c X=p-Br
d X=m-NO_2

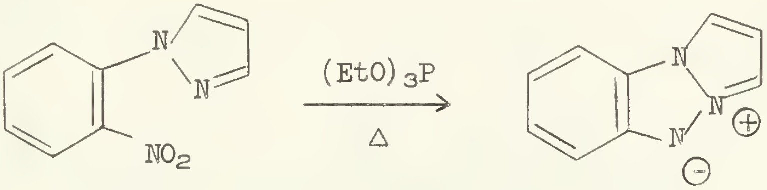


XXIa A=B=H; Z=CH_3CO, D=CH_3CO_2
b A=B=H; Z=ØCO, D=$\emptyset CO_2$
c A=B=H; Z=CN, D=Cl
d A=B=CH_3; Z=CH_3CO, D=CH_3CO_2
e A=B=CH_3; Z=ØCO, D=$\emptyset CO_2$
f A=CH_3, B=Br; Z=CN, D=Cl

Substitution reactions were found to occur when the diazapentalenides XVIIIa-c were treated with acetic or benzoic anhydride or cyanogen chloride.[15] Nmr spectral analysis of the acyl diazapentalenides indicated that disubstitution occurred at the C-1 and C-3 positions. A statistical substitution and a readily isolable diacyl

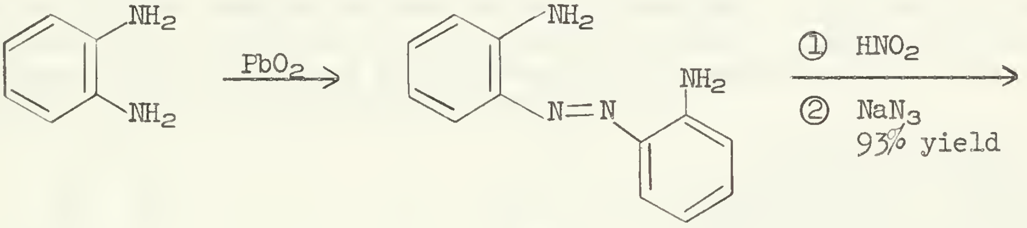
diazapentalenide could account for the 18-32% yields of products XXIa-f.

Lynch and Hung[20] synthesized benzo-1,3a,6a-triazapentalene by treating 2-(1'-pyrazolyl)-nitrobenzene with triethyl phosphite at 160° for 12 hours under carbon dioxide. The evidence cited for the triazapentalenide structure, besides its molecular formula, were the lack of a secondary NH stretching band, an nmr spectrum with a one proton triplet at τ3.34 and a six proton envelope at τ2.40-3.08 in $CDCl_3$. The triplet could be assigned to the C-2 proton which was farthest from the nitrogens on the triazapentalenide nucleus.

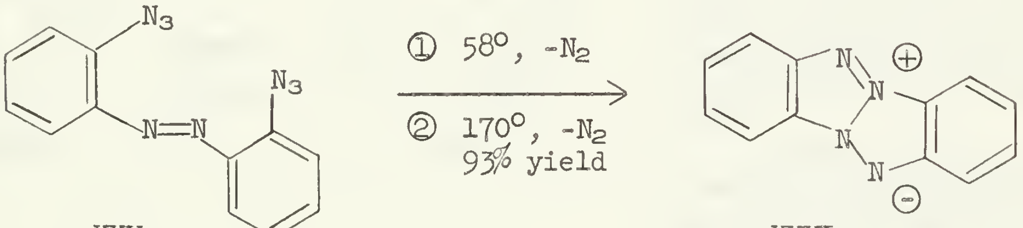


XXII XXIII

Starting with the oxidation of o-phenylenediamine, Carboni and his coworkers[21, 22] prepared 2,2'-diaminoazobenzene which was diazotized and converted to 2,2'-diazidoazobenzene which was heated to yield dibenzo-1,3a,4,6a-tetraazapentalene (DBT) XXVI.



XXIV

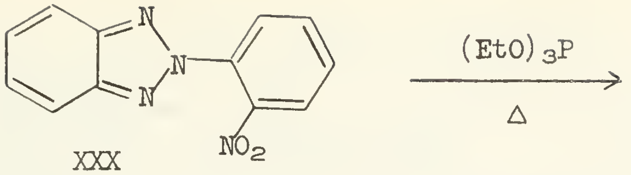


XXV XXVI

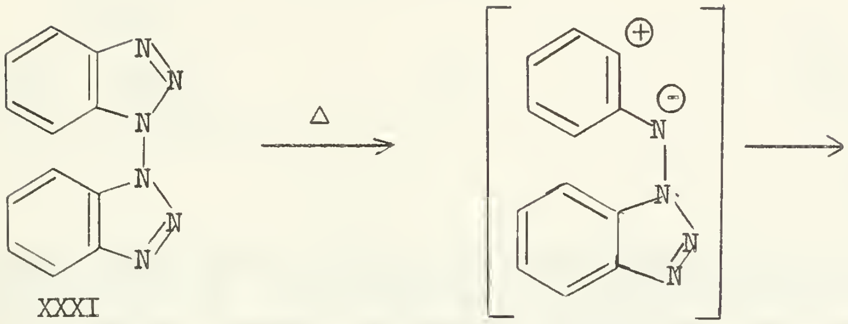
The pyrolysis of 2,2'-diazidoazobenzene occurred in two discrete stages.[22] The intermediate 2-(2'-azidophenyl)-2H-benzotriazole XXVIII was identified by its independent synthesis as follows: Oxidation of 2,2'-diaminoazobenzene with cupric sulfate in pyridine gave the 2-(2'-aminophenyl)-2H-benzotriazole XXVII which was diazotized and reacted with sodium azide to yield XXVIII.

Preliminary X-ray studies have shown that DBT is a planar molecule and has the tetraazapentalene nucleus.[23] The dipole moment of DBT in benzene was found to be zero at 25°.[22] The electronic spectrum of DBT reportedly resembled the three major bands of the isoelectronic chrysene XXIX.[22] Because the position of the maxima and the extinction coefficients are not consistently of similar magnitudes and, further, because the position of absorption of the $n \rightarrow \pi^*$ transitions were unknown, more studies on the tetraazapentalenide spectrum must be made before more satisfactory correlations can be made.

DBT was also formed from the reaction of 2-(2'-nitrophenyl)-2H-benzotriazole XXX and triethyl phosphite in 82-88% yield[24] and in 54% yield from the pyrolysis of 1,1'-bibenzotriazole XXXI.[25] In the first reaction several intermediates, ranging from a phosphinimine through a nitrene, were seen to be possible. In the pyrolysis of 1,1'-bibenzotriazole, whose structure was deduced from the products of similar reactions of model compounds, from the similarity of its ultraviolet spectrum with model compounds and from its methylation and reduction products,[25] the intermediate or transitory species XXXII was postulated in the absence of mechanistic studies.

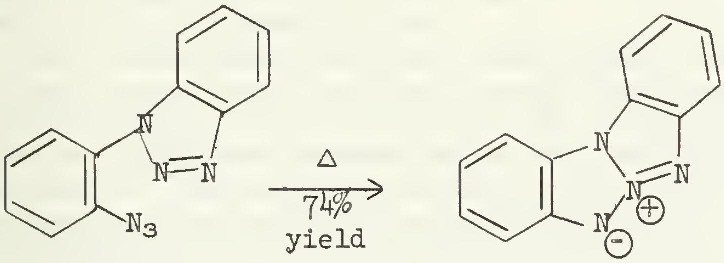


XXX XXVI

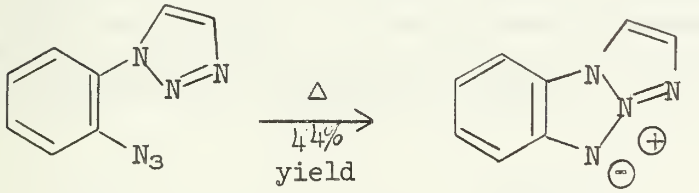


XXXI XXXII XXVI

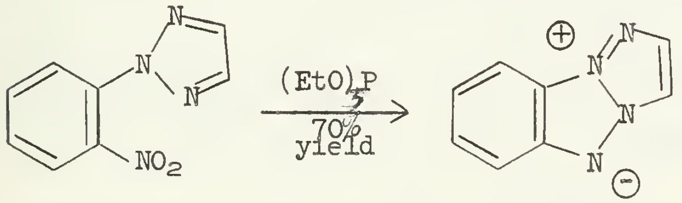
The isomeric dibenzo-1,3a,6,6a-tetraazapentalene XXXIV and monobenzo-1,3a,4,6a- and monobenzo-1,3a,6,6a-tetraazapentalenes XXXVI and XXXVIII were postulated to be formed under conditions similar to those which yielded DBT. Pyrolysis of the azides XXXIII[22] and XXXV[24] were believed to yield XXXIV and XXXVI. Monobenzo-1,3a,4,6a-tetraazapentalene XXXVIII appeared to be formed in the deoxygenative reaction of triethyl phosphite and 2-(2'-nitrophenyl)-triazole.[26]



XXXIII XXXIV



XXXV XXXVI

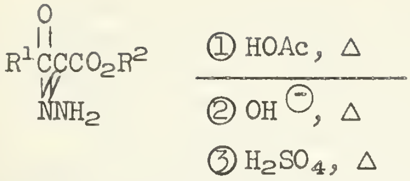


XXXVII XXXVIII

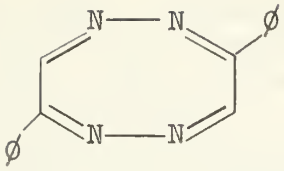
Pfleger and Hahn[27] reported the synthesis of "diphenyltetraazacyclooctatetraene" XL in 1957 which they obtained by dimerizing methyl 2-hydrazo-3-oxo-3-phenylpropanoate XXXIXa, saponifying the diester and decarboxylating the resulting acid.

Although Pfleger and Hahn noted great chemical differences in their "tetraazacyclooctatetraene" in comparison with cyclooctatetraene, i.e., heat stability, hydrogenation and the stability of the bromine to substitution in the brominated compound, it was not until after Carboni proposed the tetraazapentalenide structure that the correct structure, 2,5-diphenyl-1,3a,4,6a-tetraazapentalene XLIa (2,5-diphenyl-TAP), was assigned.[28] An X-ray study, which will be discussed later, indicated a planar molecule of the tetraazapentalene structure.[29]

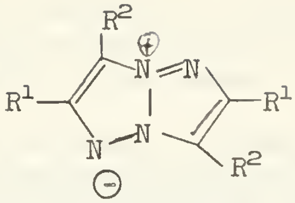
The solubilities of the tetraazapentalenides varied from the water- and ether-soluble 2,5-dimethyl-TAP, which was synthesized from ethyl 2-hydrazo-3-oxobutanoate as in the first equation on page 15,[28] to DBT



XXXIXa $R^1=\phi$, $R^2=CH_3$
b $R^1=CH_3$, $R^2=CH_3CH_2$



XL



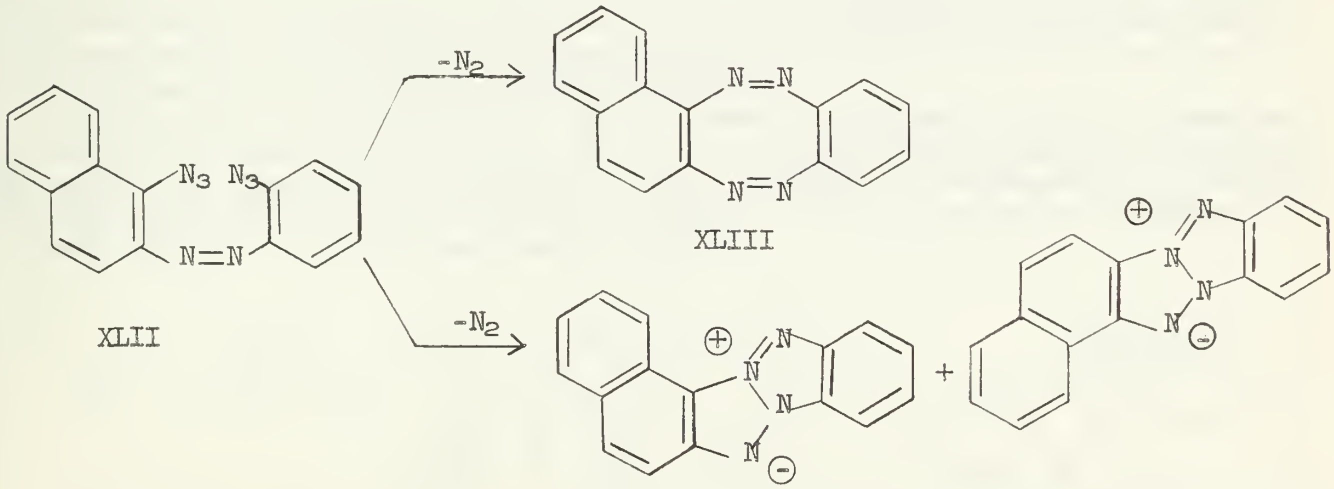
XLIa $R^1=\phi$, $R^2=CO_2H$
b $R^1=\phi$, $R^2=H$
c $R^1=CH_3$, $R^2=CO_2Et$
d $R^1=CH_3$, $R^2=CO_2H$
e $R^1=CH_3$, $R^2=H$

and its isomer XXXIV which dissolved in concentrated sulfuric acid, but not in dilute inorganic acids.[22] 3,6-Dicarbethoxy-2,5-dimethyl-TAP XLIc was soluble in carbon tetrachloride, benzene, chloroform, acetic acid and concentrated sulfuric acid, but insoluble in petroleum ether or water.[28]

The conditions for C-alkylation on the benzene ring versus those for N-alkylation on DBT were tested.[22] Treatment of DBT with n-butyl lithium followed by reaction with methyl iodide appears to give a mixture of mono-C-methylated products since the ultraviolet spectrum of monomethylated material resembled that of the starting material. Heating DBT at 150° with dimethyl sulfate or at extended periods at reflux with methyl iodide gives a cationic product whose ultraviolet spectrum reportedly shows equally blue-shifted peaks with respect to that of DBT indicating N-methylation.

The tetraazapentalenide was distinguished from the tetraazacyclooctatetraene structures unequivocally by X-ray study. The chemical relationship between DBT and dibenzotetraazacyclooctatetraene COT was investigated. The nmr spectrum of a solution of DBT was reported as an ABCD pattern containing a minimum of fifteen lines which is temperature independent up to 225°.[22] The nmr spectrum appears to be rationalized better with the DBT structure than with the COT one. However, the possibility that part of the spectrum is due to COT cannot be ruled out.

Chemical evidence to distinguish between DBT and COT confirmed the former structure for at least ambient temperatures. Assuming random ring closure to the azacyclooctatetraene or to the azapentalenide systems, one would, perhaps, have expected only one detectable naphthobenzotetraazacyclooctatetraene XLIII from XLII, but, perhaps, two naphthobenzotetraazapentalenides XLIV and XLV. (Because of the possibility of cis-trans azo bond isomerism, it is not possible to conclusively rule out isomerism in XLIII).



XLII

XLIII

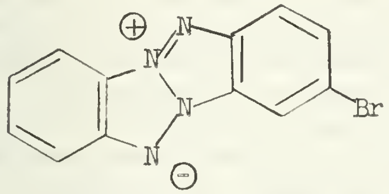
XLIV

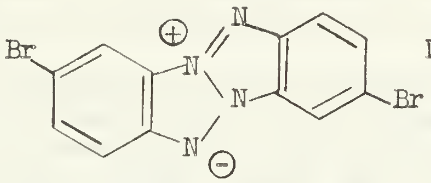
XLV

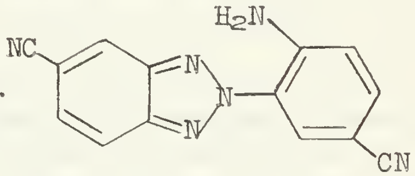
Pyrolysis of XLII[22] produced a solid which had a wide melting point range 192-220°, but analyzed for $C_{16}H_{10}N_4$. Chromatographic separation of the material gave two sharp melting solids, melting points of 211.5-212.5° and 244.5-245°, (stable at their melting points) whose infrared spectra, when summed, correlated with the infrared spectrum of the mixture.

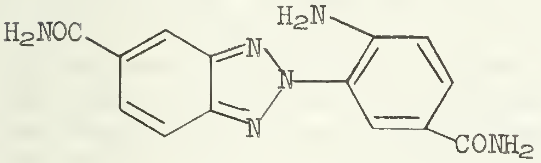
Under conditions of electrophilic substitution reactions of aromatic compounds, substitution was found to occur on the tetraazapentalenide nucleus. 3,6-Dibromo-2,5-dimethyl-TAP XLVII formed in 90% yield after treating 2,5-dimethyl-TAP XLId with two equivalents of bromine. When 2,5-dimethyl-TAP was mixed with concentrated sulfuric acid and concentrated nitric acid, 2,5-dimethyl-3,6-dinitro-TAP XLVI was isolated in 50% yield.[28]

An indication of the directing effects of the tetraazapentalenide system was noted in the bromination of DBT. Bromination of DBT XXVI with N-bromosuccinimide gave a mixture of monobromo-DBT XLVIII and dibromo-DBT XLIX in 70% and 5-10% yields respectively.[26]


XLVIII


XLIX


LI

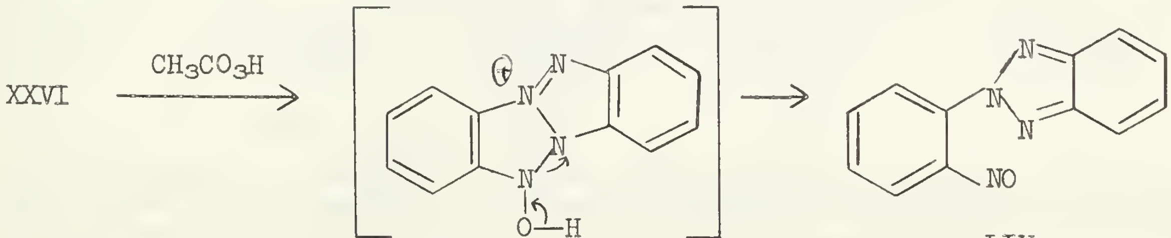

LII

The positions of substitution[26] were determined by the independent synthesis of monobromo-DBT by pyrolysis of 2-(2'-azido-5'-bromophenyl)-2H-benzotriazole L and by the partial degradation of dibromo-DBT to a product which was identical to the independently synthesized compounds LI and LII. In the discussion of ring opening with cuprous cyanide, it will be shown that substitution and ring opening occur in the reaction of the dibromo-DBT with cuprous cyanide.

The valence bond structures of the "intermediates" in the substitution reaction appear to be in accordance with the bromination in that the lower energy species are formed giving greatest resonance interaction with the more negative nitrogens in the system.

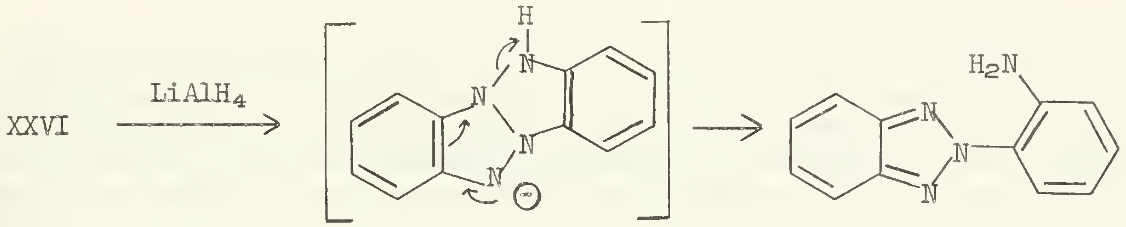
Cleavage[26] of the tetraazapentalenide nucleus occurred on reacting DBT or monobromo-DBT XLVIII with cuprous cyanide in refluxing base. Thus, DBT gave 2-(2'-amino-5'-cyanophenyl)-2H-benzotriazole and monobromo-DBT gave 2-(2'-amino-5'-cyanophenyl)-2H-benzotriazole, which was found to be identical to the saponified 2-(2'-acetamido-5-cyanophenyl)-2H-benzotriazole and whose acid hydrolysis product, 2-(5'-acetamido-2'-aminophenyl)-2H-benzotriazole, was identical with that from 2-(2'-acetamido-5'-cyanophenyl)-2H-benzotriazole.

3,6-Dicarboxy-2,5-diphenyl-TAP did not decolorize aqueous, alkaline permanganate even after standing in it for a day; however, 2,5-diphenyl-TAP or 2,5-dimethyl-TAP readily decolorized permanganate.[28] DBT was stable to permanganate in acetone, but readily reacted with peracetic acid to yield 2-(2'-nitrosophenyl)-2H-benzotriazole through the postulated species LIII.[26]



LIII
LIV

Reduction[26] of DBT with lithium aluminum hydride was postulated to proceed through LV to yield 2-(2'-aminophenyl)-2H-benzotriazole XXVII. A phosphorus-hydroiodic acid reduction[27] gave 5-phenyl-1H-triazole, ammonia and ethyl benzene from 2,5-diphenyl-TAP.



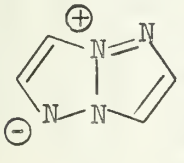
LV XXVII

The dibenzo- and monobenzo-tetraazapentalenides were found to have substantial resonance energies indicating aromaticity of the tetraazapentalenide system. Basing the energy of the localized double bond structures on XXVI and XXXIV (and the corresponding monobenzo structures), Chia and Simmons[30] calculated resonance energies from heats of combustion data of 122.9 kcal/mole for DBT, 133.6 for XXXIV, 85.9 for XXXVIII and 94.0 for XXXVI.

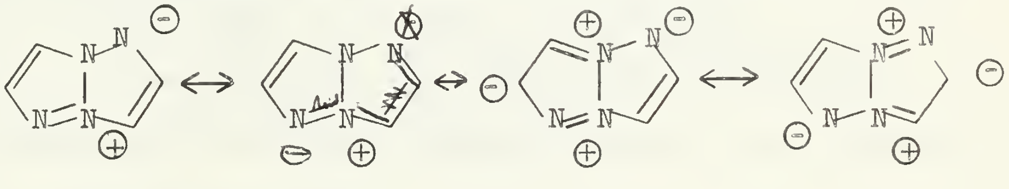
The length of a bond intermediate between that of a pure CC multiple bond and that of a CC bond of one less unsaturation is an indication of resonance interaction, although not necessarily of aromaticity.[31] The interatomic distances[29] of the rubidium salt of 3,6-dicarboxy-2,5-dimethyl-TAP were found to be as follows: bond 1-2 (CN), 1.36 A; bond 2-3 (CC), 1.33 A; bond 3-3a (CN), 1.38 A; bond 3a-6a (NN), 1.24 A; and bond 1-6a (NN), 1.28 A. The CC bond length is the same as that found in ethylene, 1.33 A. The CN bond lengths of 1.38 A and 1.36 A corresponded quite well with the CN bonds in pyridine 1.37 A or pyrrole 1.38 A. The NN bond lengths are roughly about the length of the internal NN bond 1.24 A in diazomethane or of the NN bond 1.23 A in azobenzene.[32] (The NN bond length in the difluoride salt of hydrazine is 1.42 A.)[33] There appears to be considerable resonance interaction between the conjugated bonds of the rubidium salt of 3,6-dicarboxy-2,5-dimethyl-TAP, except for the CC double bond which is the same length as the double bond in ethylene.

When the structure LVI was used to calculate HMO energies and bond orders for 1,3a,4,6a-tetraazapentalene with the parameters $\alpha_{\dot{N}} = \alpha_c + \beta_{cc}$ and $\alpha_{\ddot{N}} = \alpha_c + 1.5\beta_{cc}$ with all $\beta_{xc} = \beta_{cc}$, where α_X is the Coulomb integral of atom X, β_{xc} is the resonance integral of the atoms XC, $\ddot{N}$ represents the pyrrole-like nitrogen which formally contributes two electrons to the π-electron MO and $\dot{N}$ similarly represents a pyridine-like nitrogen, it was found that the nonbonding electrons of pentalene dianion became bonding electrons in the tetraazapentalenides and that the greatest π-bond order (0.739, within the range of bond orders for aromatic bonds)[34] was found at the CC bonds.[30] A delocalization energy of 4.421β was calculated for LVI.

Chia and Simmons[30] tried to improve their results by statistically weighting the Coulomb and resonance integrals of the nitrogens in LVI according to the times they occurred in various valence states in all the singly and doubly positively and negatively charged canonical structures, e.g., LVII, LVIII and LIX, LX (weighted 0.1 of the value of the singly positively and negatively charged structures).

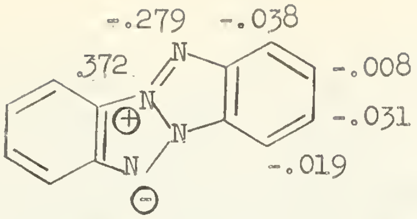


LVI



LVII LVIII LIX LX

The delocalization energies[30] of XXVI, XXXIV, XXXVIII and XXXVI were found to be 7.905β, 8.004, 6.151 and 6.213. The larger delocalization energies of the 1,3a,6, 6a-tetraazapentalenides compared to the 1,3a,4,6a-tetraazapentalenides are consistent with the resonance energies.



LXI

Charge distributions[30] were calculated for the benzotetraazapentalenes, and that for DBT is reproduced on structure LXI. The slightly more negative positions on the benzene rings ortho to the more negative nitrogens as compared to the para positions are not in accord with the bromination results, if the substitution reaction parallels the electron density of the ground state and if only electronic factors were significant.

The evidence available for judging the aromaticity of the azapentalenes are none; that for the azapentalenides were the pKa values and resonance energies. Due to its time limitations, the nmr spectra of the azapentalenides could not be used conclusively to distinguish between protons on a conjugated, localized system with little resonance energy or on a conjugated, delocalized or aromatic system.

The monoazapentalenide XIII did not appear to be aromatic according to its basicity. The diaza-bridged azapentalenides, except for XXIII whose basicity was not reported, on the basis of their basicity to aqueous bicarbonate (see XVIIIa-c and XXa-d) and their solubility in strong mineral acid (see DBT and XXXIV) appear to be unusually stabilized; however, the relative contribution from aromatic and electrostatic effects among others are not apparent.

The resonance energies found for the benzotetraazapentalenides indicate that the tetraazapentalenide system is aromatic. More studies, *e.g.*, the determination of resonance energies, of diamagnetic susceptibilities or the presence of ring currents, on the other azapentalenides must be conducted to see if they are also aromatic.

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RING CURRENTS IN CYCLIC ORGANIC MOLECULES

Reported by Terry G. Burlingame October 9, 1967

INTRODUCTION

The concept of ring current in cyclic unsaturated systems was first used by Pauling[1] to explain the abnormally large diamagnetic susceptibility parallel to the hexagonal axis in benzene. The hypothesis was advanced that this observed susceptibility arises from the Larmor precession of the six π-electrons in orbits including many nuclei equivalent to a "superconducting current" I flowing in a ring with radius equal to that of the benzene ring. Pople[2] later used this classical "free electron" model to rationalize the large downfield nuclear magnetic resonance shift of the protons in benzene relative to those in ethylene. Figure 1 shows the mechanism advanced by Pople to explain this "abnormal" deshielding effect. H_o induces a current I near the plane of the ring. The resultant magnetic field due to this current assists the applied field in the region of the ring protons, and a smaller field than usual is sufficient to bring them into resonance; thus we have deshielding relative to normal olefinic protons. This same scheme predicts that groups held sterically above or below the ring plane will be abnormally shielded (i.e., their protons will come into resonance at higher applied fields than normal).

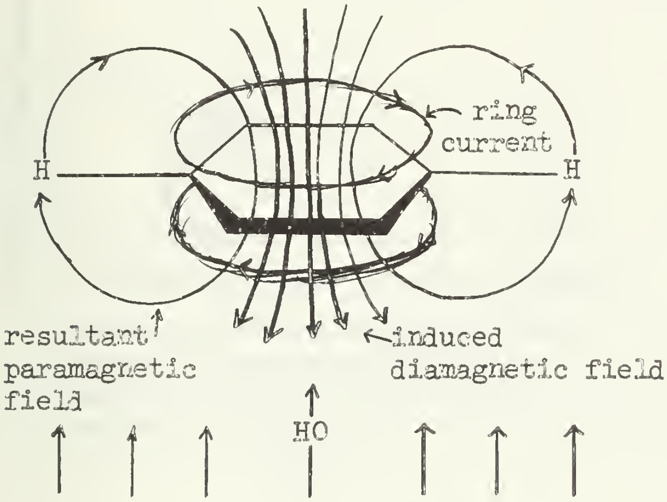


Fig. 1 (after Dyer[3])

In this seminar we shall trace in a rather descriptive manner the development of the theory of ring currents in cyclic molecules, including an objection or two to the theory in general and the proposal of a different type of ring current for non-aromatic systems. The remainder of the seminar will evaluate the success of the theories in explaining and predicting the experimentally observed properties of a representative number of cyclic molecules, and we shall concern ourselves with questions regarding the relationship of ring currents to other molecular properties.

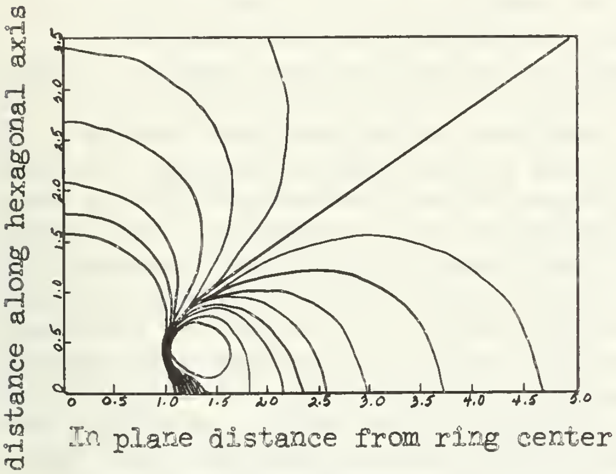
THEORY - CLASSICAL APPROACHES

Pauling's classical approach to ring current theory[1] pictured the six π-electrons precessing about the benzene ring in a magnetic field H_o perpendicular to the ring plane as a superconducting current I, the magnitude of which is given as follows:

$I = -ne^2H_o/4\pi mc$ where n=no. of electrons
e=charge of an electron
m=mass of electron
c=speed of light

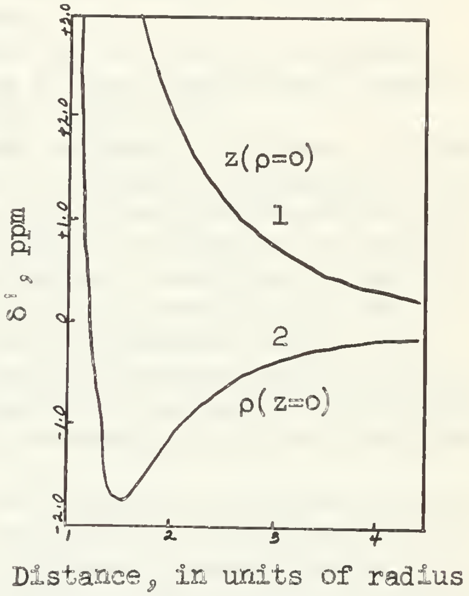
Pople,[2] in applying this "free electron" model to an interpretation of the nmr spectra of polynuclear hydrocarbons, replaced this diamagnetic current (which was, incidentally, taken in the plane of the ring) by an equivalent point dipole of magnitude $3e^2H_oa^2/2\pi mc^2$ at the center of the benzene hexagon, where $\underline{a}$ is the C-C bond distance, and then averaged the strength of this dipole over all possible orientations of the molecule with respect to the applied field. The calculations of Pople were refined somewhat by Waugh and Fessenden[4] and Johnson and Bovey[5] while still preserving their classical basis. These workers considered the magnetic field which would arise from $\underline{n}$ electrons circulating in a loop of radius $\underline{a}$, recognizing that the π-electron cloud was not confined to the plane of the ring, but consisted of two doughnut-like rings on either side of the ring plane. The induced magnetic field was again

averaged over all orientations of the molecule with respect to the applied field. Using the separation of the current rings as a parameter in the equation, Waugh and Fessenden found they could obtain values of δ', the "aromaticity shift" of benzene (evaluated as 1.50 ppm) with respect to suitable olefinic models, if the current ring separation was set at 0.9 A°. Johnson and Bovey,[5] using a more correct expression, calculated the current separation to be 1.28 A° and constructed diagrams (Figures 2 and 3) showing the diamagnetic or paramagnetic shift predicted for a proton in any position relative to an aromatic ring on the basis of the free electron model.



shielding and deshielding lines shown in one quadrant of a plane passing normally through the center of the ring

Fig. 2



change in shielding as a function of distance (1) along hexagonal axis (2) from the center in the ring plane

Fig. 3

QUANTUM MECHANICAL APPROACH

London[6] developed a quantum mechanical theory of ring currents for a planar cyclic molecule with all carbon atoms equivalent. An independent electron model of the type developed by Hückel was used, and the effect of introducing a magnetic field H perpendicular to the ring plane was calculated. Application of the theory to a hydrocarbon of alternating bond lengths requires the use of two resonance integrals β_1 and β_2. The energies ϵ_j of the occupied MO's for a cyclic hydrocarbon C_MH_M (M even) may then be derived in terms of β_1, β_2, and the area of the ring. The magnetic susceptibility due to the ring current is obtained by differentiating the total energy twice with respect to the magnetic field strength.

Pople and Untch[7] have derived expressions for the induced current for a monocyclic conjugated hydrocarbon with alternating bond lengths in terms of λ, the ratio $\beta_1/\beta_2 \leqslant 1$, defined as an alternation parameter. The derived expression for the induced current contains terms which change sign as M varies from 4n to 4n + 2, and the following points may be noted from the rather complex expression which results:

1. For M = 4n + 2 we get a negative contribution to the susceptibility (diamagnetic ring current), but for M = 4n we get a positive contribution (paramagnetic ring current).

2. The magnitude of the ring currents is reduced if bond alternation occurs. The larger the ring, the greater is the reduction of ring current for a given amount of alternation.

3. For 4n rings a first order change in energy with magnetic field is predicted if no alternation occurs. However, in this situation the highest occupied and lowest

unoccupied MO's become degenerate, and 4n systems should alternate their bond lengths (distort) in order to remove this degeneracy. This is a manifestation of the Jahn-Teller effect.

4. Diamagnetism is predicted for 4n + 2 rings as well as an increase in current with increasing M = 4n + 2 in the absence of alternation. Dewar and Gleicher[8] have calculated that significant alternation may be expected for M = 4n + 2 = 26 and larger rings.

In addition, the following points are also noteworthy:

1. Rings with large M will be nonplanar and buckled; the resulting less effective overlap of the 2pπ atomic orbitals as well as the smaller projected area of the ring will reduce the magnitude of the ring current.

2. Theoretical chemical shifts could in principle be obtained by a method similar to that used by Johnson and Bovey for benzene if the geometry and degree of bond alternation in systems of large M could be better specified.

Musher[9] has objected to the whole concept of ring currents in general, claiming that the magnetic susceptibility and chemical shifts of aromatic hydrocarbons can be just as well represented as the sum of contributions from localized electrons of both σ and π character. His criticism of London's LCAO-MO development is based on the argument that London's proof that the σ electrons give no contribution to the magnetic susceptibility (ring current) is because of the arbitrariness of the functions he used to set up the problem of a molecule in a magnetic field. A mathematical argument is offered which according to Musher demonstrates that the susceptibility is independent of whether the electrons are localized or delocalized, and calculated values for the magnetic susceptibility assuming localized contributions agree well with experimentally determined values.

Gaidis and West have criticized Musher's model of locally anisotropic carbon atoms on the basis that it fails to predict large upfield shifts for protons in the center of an aromatic ring (an experimental fact). Classical representations of Musher's model (Figure 4) predict a large downfield shift for protons near the center as opposed to the ring current model, which correctly predicts the upfield shift.

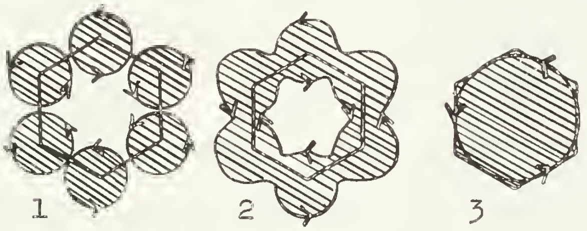


Fig. 4 Musher's model (1 or 2) and the ring current model
Protons are shifted upfield in the shaded regions.

The authors also believe that Musher's proof fails to show that a localized model gives the same results as a delocalized one although Musher[11] has again justified his conclusions and leveled criticisms at the "theoretically unjustifiable" approximations which MO theory uses to predict ring currents.

Centered between the two extremes in ring current theory is a development by Pople and Ferguson[12] using MO theory to calculate the contributions of local intra-atomic currents from electrons on the carbon atoms of aromatic compounds. Their results suggest that the magnitude of these contributions is 30-50% of the "aromaticity shift" of the ring protons in benzene. This result reduces considerably the magnitude of the effects ascribed to ring currents.

EXPERIMENTAL EVIDENCE

General Considerations - Nuclear magnetic resonance spectroscopy has become a valuable tool for examining experimentally the problem of a planar unsaturated cyclic molecule in a magnetic field. Numerous experiments may be cited from the literature which seem to support the general contention that "ring current" is a real phenomenon. In this section we shall examine various model compounds which seem to demonstrate the effects generally attributed to ring currents; a later section will deal with

more quantitative attempts to correlate the theories of ring current and aromatic stability with some of the experimentally determined nmr parameters.

Examination of the nmr spectra of compounds known as polymethylene benzenes provided early workers with convincing evidence supporting the classical ring current model. These molecules contain methylene groups which are sterically held above the aromatic ring plane. Figure 5 shows shifts upfield from benzene for the central methylene protons of two representative 1,4-derivatives and 1,2-hexamethylene benzene.[13] The central methylene protons in the 1,2-hexamethylenebenzene absorb in the region characteristic of saturated cyclic hydrocarbons.

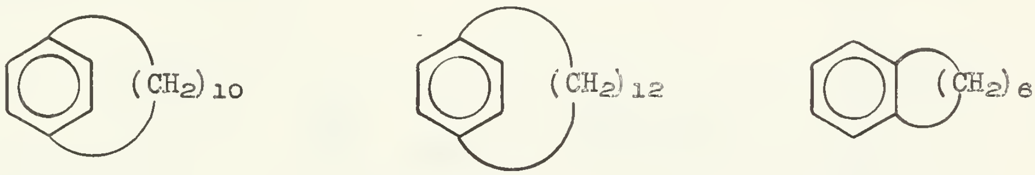
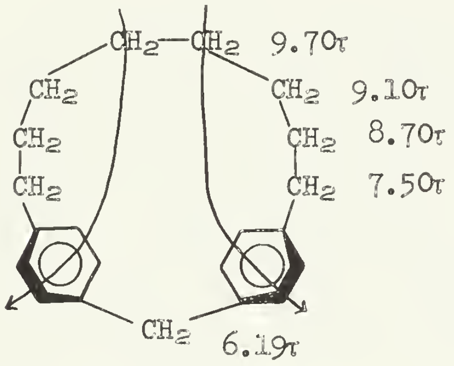


Fig. 5 6.50 ppm 6.30 ppm 5.8 ppm

Figure 6 shows [1.8] paracyclophane which shows an even more striking shielding effect for the methylene protons above the aromatic ring planes. Examination of models of the foregoing compounds, however, shows that it is not clear whether the observed τ values are best rationalized by a ring current effect or as the sum of local contributions on each carbon atom. An even more convincing model compound on which the Musher interpretation fails is trans 15,16-dialkyldihydropyrene, the methyl and ethyl derivatives of which have recently been synthesized.[14,15] Figure 7 summarizes the spectral data for these compounds. The methyl and ethyl groups both appear at very high fields. In both these compounds the alkyl groups are presumably within or protruding out from the cavity of the π electron cloud surrounding the periphery of the molecule. This time the ring current model correctly predicts the high field shift; the Musher model does not. Notice further that in the ethyl derivative the CH_2 protons come at higher field than the CH_3 protons, opposite to the order normally observed. Again, this is in accord with the stronger shielding closer to the ring plane along the Z axis which the ring current model predicts.



[1.8] paracyclophane
(after Dyer)[3]
Fig. 6 (τ values assume TMS reference)

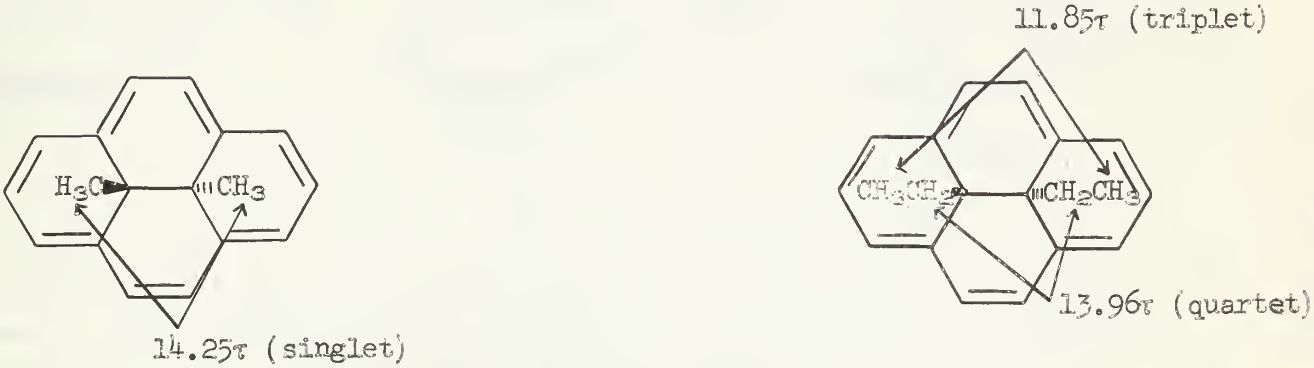
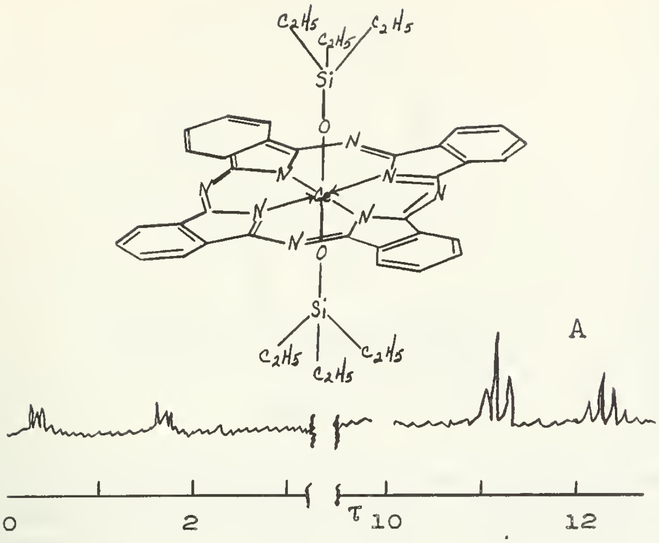
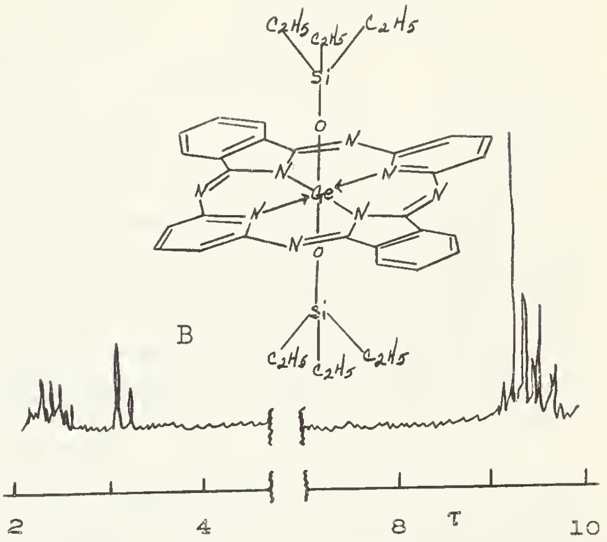


Fig. 7

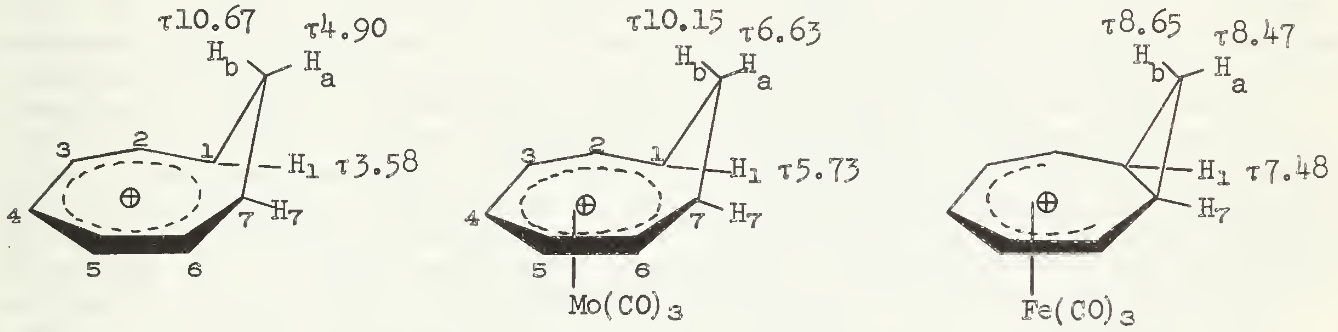
A further example of this effect is given by comparison of the nmr spectra of the germanium phthalocyanine and hemiporphyrazine derivatives shown in Figure 8.[16] The phthalocyanine derivative(A) shows the striking effects of ring current shielding of the ethyl groups while the structurally similar hemiporphyrazine (B)





derivative does not. These results are in order with conclusions by other workers regarding bond alternation and non-planarity of the ring in the hemiporphyrazine derivative. Note that methylene protons are again at higher field than methyl protons in the ethyl groups of the phthalocyanine derivative in accordance with the ring current model of shielding (recall Figure 3).

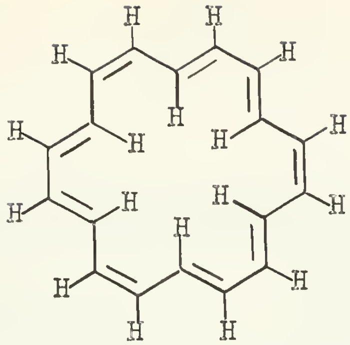
The work of Winstein and co-workers on homotropylium ion and its derivatives[17] has provided evidence for ring currents in "nonclassical" aromatic compounds. Compounds such as A (Figure 9) can have a cyclic delocalized π system only by virtue of orbital overlap of a type intermediate between σ and π between C_1 and C_7. The nmr data for these ions, formed by protonation of the appropriate cyclooctatetraene derivatives in concentrated H_2SO_4, are summarized in Figure 9 and are consistent with the proposed structures of these ions. Note in particular the large chemical shift difference for H_b and H_a in compounds A and B but not in C. Calculation of the chemical shift difference H_b-H_a expected for A using the data of Johnson and Bovey (Figure 3) gave 5.56 ppm, in good agreement with the observed results. Compound C is postulated to be non-homoaromatic because the iron atom prefers to coordinate to a 4π-electron system rather than the 6π-electron system needed for homoaromaticity.



A B C

Fig. 9

Another compound which demonstrates both shielding and deshielding effects as predicted by the ring current model is [18] annulene (Figure 9).[18] This compound is planar from x-ray studies (<.1A° deviation from planarity) and shows little bond alternation. Its nmr spectrum at -60° shows the inner protons at abnormally high field and the outer ones at abnormally low field in accordance with the usual ring current model.



at -60°: inner H=τ12.99
outer H=τ 0.72

Fig. 9

Recall that the molecular orbital theory of Pople and Untch[7] predicted that in the absence of large bond alternations or deviations from planarity, conjugated monocyclic systems with 4n + 2 π-electrons (like [18] annulene) will show a diamagnetic ring current, but those with 4n π-electrons should show a paramagnetic ring current. Compounds showing paramagnetic ring currents should have protons inside the ring or above the ring plane at abnormally low field and those outside the ring at abnormally high field- the exact opposite of the effects in benzene-like compounds. Are there any experimental results which confirm this prediction?

Pople and Untch[7] examined the reported nmr spectra of four annulenes (shown in Figure 10) for the effects of induced paramagnetic ring currents. The spectra are summarized below each figure. The lowest field signal belongs to the inner protons of compounds I-III, but by integration this position in I and II seems to be an averaged value due to rapid rotation of the trans double bonds. A proton attached to these bonds then spends half its time inside and half outside the ring. However, no such averaging could be detected for III, and it has been suggested[18] that the trans double bonds may be perpendicular to the rest of the ring plane in these compounds. Variable temperature studies to distinguish these two possibilities have now been carried out;[19] the results show that rotation of the trans double bonds does indeed occur in I and II and that the inner protons absorb at even lower field than indicated above. Thus the experimental results tend to indicate an induced paramagnetic ring current. Realizing that the objection that the observed shifts are due to the local diamagnetic anisotropy of the triple bonds might be a valid one, Pople and Untch calculated the maximum local anisotropy effects which could be expected in these molecules, and compared calculated chemical shifts (using cyclohexene, τ4.4, for model olefinic protons) with the observed values (Table I). These results suggest that local anisotropy effects do not account for all of the downfield shifts in compounds I-III.

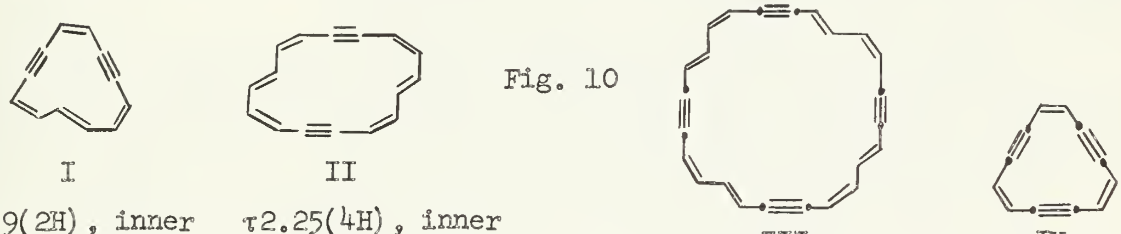


Fig. 10

I

τ-.9(2H), inner
4.97(2H)
5.47(2H) outer
5.82(2H)

II

τ2.25(4H), inner
4.35(4H)
4.93(4H) outer

III

τ1.80(4H), inner
3.6-5.0(12H), outer

IV

τ5.55(6H), outer

Table I Maximum Calculated Local Anisotropy Shifts (from cyclohexene, τ4.4)

Compound	Protons	$\Delta\tau$calc. from cyclohexene (τ4.4)	τcalc.	τobs.
I	inner	-1.48	2.92	-.9
II	inner	-1.51	2.89	2.25
III	inner	-0.57	3.83	1.80
IV	outer	+1.24	5.64	5.55

Although τcalc. agrees well with τobs. for IV, the authors contend that the results are best explained by paramagnetic ring currents since the model compounds shown in Figure 11 have their corresponding hydrogens at τ4.3 instead of the value 5.64 calculated above.

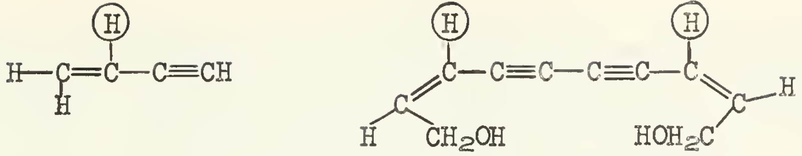
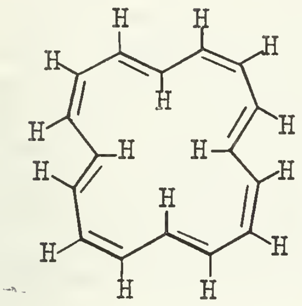


Fig. 11

The low temperature nmr spectra of two other annulenes gives evidence for paramagnetic ring currents in certain 4n π-systems. At -120°C, [16] annulene (Fig. 12) shows a 4 proton peak at τ-.32 (triplet, inner H) and a 12 proton peak at τ4.8 (multiplet, outer H).[20] [24] annulene at -80° shows the inner protons at τ-2.9 to -1.2 and the outer ones at τ5.27,[21] again consistent with the MO theory of paramagnetic ring currents.



[16] annulene
Fig. 12

QUANTITATIVE CORRELATIONS - THE PREDICTION OF CHEMICAL SHIFTS

Waugh and Fessenden[4] constructed models of the polymethylene benzenes mentioned earlier and calculated shielding effects for the methylene protons using the classical free electron model. Fairly good agreement with experiment was obtained, although Johnson and Bovey later pointed out[5] that their equation was off by a constant factor. Predictions made by Johnson and Bovey[5] on the basis of their model (2 current loops separated by 1.28A°) are summarized in Table II. Notice the very poor agreement between experiment and theory for diphenylmethane and napthalene. The polynuclear aromatic hydrocarbons have consistently frustrated the attempts of workers to predict accurate chemical shifts for them. As Table III shows for napthalene, the difference between experiment and theory has lessened with increasing degree of sophistication of theory, but it is still far from zero.

Table II Calculated vs. Observed Values (Johnson and Bovey)

Compound	Group	τobs.	τcalc.
Toluene	CH_3	7.66	7.52
Ethylbenzene	CH_3	8.80	8.79
Cumene	CH_3	8.77	8.79
Tetralin	α-CH_2	7.30	7.34
	β-CH_2	8.22	8.07
Dibenzyl	CH_2	7.05	7.11
Diphenylmethane	CH_2	6.08	6.58
Naphthalene	α-CH	2.27	2.03
	β-CH	2.63	2.46

Table III Observed vs. Calculated τ Values for Napthalene

Method	Hydrogen	τobs. - τcalc. (ppm.)
Classical	α	.24
	β	.17
Hückel-MO	α	.24
	β	.25
SCF-MO	α	.18
	β	.18

The recent findings of Pople and Ferguson[12] that about 30% of the diamagnetic anisotropy of benzene is due to local atomic contributions should close the gap between theory and experiment somewhat.

THE RELATION OF RING CURRENT TO AROMATICITY

It has been 140 years since the discovery of benzene, yet chemists are still arguing about the exact definition of aromaticity. The classical definition

"showing benzene-like stability and chemical behavior" is a poor one since chemical reactivity is often an ambiguous criterion.[18] Sondheimer[18] and others have proposed a "modern" definition of aromaticity as "having a measurable degree of cyclic delocalization of the π-electron system in the ground state of the molecule." In view of the fact that paramagnetic ring currents may exist in 4n annulenes due to π-electron delocalization, it seems that this definition should be restated. The most comprehensive modern definition states that "a monocyclic compound is considered to be aromatic if the compound has a cyclic, delocalized orbital that has a number of π-electrons in keeping with Hückel's rule, is reasonably planar, and has greater stabilization by π-electron delocalization than does an analog with localized bonds."[22] Other experimentally determinable criteria are non-alternate carbon-carbon bond lengths and ability to sustain a diamagnetic ring current in an applied magnetic field. Elvidge[23] and Sondheimer[18] have proposed that the latter criterion be considered the "modern" criterion for aromaticity. The question then arises, is there any direct relation between the magnitude of the ring current and the "aromaticity" of a compound as evaluated by some other means?

In an early attempt to correlate aromaticity and ring current Elvidge and Jackman[24] concluded from an nmr study of substituted 2-pyridones (Fig. 14) that these compounds had about 35% of the aromaticity of benzene, although there was no thermodynamic data available which would support this conclusion.

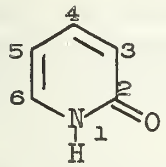


Fig. 14 2-Pyridone

Elvidge[23] later attempted to assess the aromaticity of 2-methylfuran, 2-methylthiophene and 2-methylpyrrole by the following method: Starting with the end-of-chain methyl in a long conjugated polyene and correcting for the inductive effects of the respective heteroatoms using diethyl ether, ethyl methyl sulfide, and sec-butylamine, he calculated chemical shifts to be expected from the 2-methyl groups in the absence of ring current effects. Comparison with experimental values gave the "ring current shifts" which were then compared to toluene by correcting for the differences in ring areas and proton distances using the equivalent dipole

$$\frac{i_M}{i_T} = \frac{\Delta_M}{\Delta_T} \cdot \frac{A_T}{A_M} \left(\frac{R_M}{R_T}\right)^3$$

approximation where M refers to the molecule in question, T refers to toluene and i, Δ, A, and R are the ring current, the ring current shifts, the area of the ring and the distances of the protons from the ring center, respectively. Ratios of .46, .75, and .59 were obtained for furan, thiophene, and pyrrole, respectively. Since these values were in the same order as the experimentally determined resonance energies, Elvidge concluded that ring current and aromaticity were directly related.

Abraham and Thomas[25] have recently criticized Elvidge's work and undertaken a systematic analysis of the relation of ring currents to resonance energy. These authors conclude from their studies that the magnitude of the ring currents in furan and thiophene is not very different from that in benzene. The difference between their results and Elvidge's lies in the choice of non-aromatic models and allowance for local atomic contributions to the observed "aromaticity shift" in benzene. Elvidge's use of a long-chain polyene for a model representing localized cyclohexatriene is discounted on two points: (1) There is no reason to expect that bond-alternation in polyenes is minimal (recent theory also supports this criticism);[8] (2) The geometries of a polyene and hypothetical cyclohexatriene are entirely different with respect to the configurations of the double bonds; thus the shielding effects due to these double bonds will be different. Abraham and Thomas thus use cyclohexadiene and 2-methylcyclohexa-1,3-diene as localized models to compare with benzene and toluene respectively after correcting for effects due to introduction of the third double bond in the ring system and due to local atomic contributions. The ring current shifts in furan and thiophene were evaluated by using the 4,5-dihydro- and 2-methyl-4,5-dihydro-derivatives as localized models of the respective aromatic compounds and assuming that local anisotropy contributions were about the same as that in benzene. The equivalent dipole approximation was again used to obtain the ring current ratios. Results are shown in Table IV.

Table IV

Compound	Evaluated Ring Current Shift	i/i Benzene	RE (kcal)
Benzene	.85 (ring protons)	1.0	36-41
Toluene	.52 (CH_3 protons)	1.0	
Furan	.73 (ring protons)	1.0	17-26
2-methylfuran	.45 (CH_3 protons)	1.1	
Thiophene	.75 (ring protons)	1.0	29-31
2-methylthiophene	.49 (methyl protons)	1.1	

Considerable support for Abraham and Thomas' method comes from the fact that the same results are obtained from evaluation of ring current shifts for both ring protons and methyl protons, while Elvidge's method fails completely when applied to the 2-H protons.

Dewar and Gleicher[8] have recently predicted from MO theory that [22] annulene will be aromatic but that because of bond-alternation [26] annulene and higher 4n + 2 annulenes will not be aromatic. Sondheimer and Leznoff[26] have recently prepared a tridehydro [26] annulene which in accordance with the predictions of Dewar and Gleicher does not appear to be aromatic. Thus the nmr shows only a broad multiplet ($\tau 2.0-4.5$) and cooling to -60° causes no change in the spectrum. Preliminary investigations on some [30] annulene derivatives have given essentially the same results, suggesting that a diamagnetic ring current may indeed be a very sensitive test for aromaticity as we now understand it.

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THE SKELL THEORY

Reported by Herbert G. Seto October 12, 1967

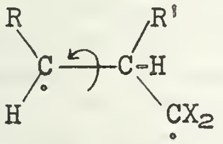
INTRODUCTION

Within the past decade, carbenes ($R_2C:$), as reaction intermediates, have received a great deal of attention. It was recognized in the early study of carbenes that knowledge of spin and ground states of the intermediate species would be helpful in explaining reaction products. P. S. Skell was the first worker to propose a spin state theory for carbenes based on the chemical evidence of carbene addition to olefins and insertion into C-H bonds. More recently, nitrenes have appeared in the literature,[1] and the so-called Skell theory has successfully been applied to nitrene intermediate spin states. This seminar will deal with Skell's hypothesis and some of its applications to carbene chemistry. The viewpoint will be largely from that of addition reactions. A review of the early literature pertaining to Skell's hypothesis can be found in Kirmse's "Carbene Chemistry."[2]

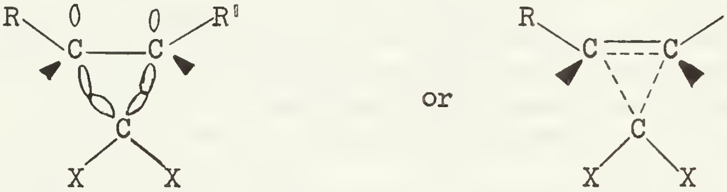
THE FORMULATION OF SKELL'S THEORY

Addition reactions of carbenes to carbon-carbon double bonds and insertion reactions in carbon-hydrogen bonds have been studied extensively to discover the chemical nature of singlet and triplet carbenes. Skell and Garner[3] found that the reaction[4] of cis- or trans-2-butene with alcohol-free potassium t-butoxide and bromoform at -10° C. proceeded in a stereospecific fashion with the products cis- and trans-2-butene respectively.

On stereochemical grounds, two intermediates were considered likely. Since $\cdot CH_2CH_2CH_2\cdot$ has an appreciable half-life in the gas phase,[5] the formation of (I) as a relatively stable intermediate from the association of C_4H_8 and triplet $:CX_2$ was possible. (I) should equilibrate among the diastereomeric radicals through rotations and inversions as rapidly as the radical obtained from the reaction of $\cdot CCl_3$ with the 2-butenes[6] to give a mixture of isomers.



I



II

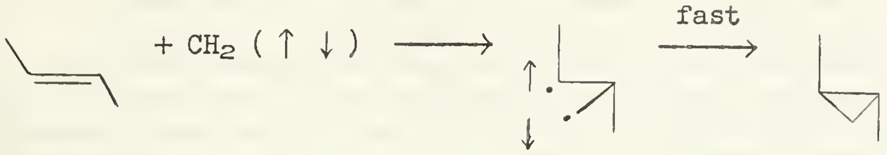
The second possibility was that $:CBr_2$ with a singlet spin state bonded simultaneously with both carbons of the double bond (II) to give the corresponding isomer. Skell felt that he had predominantly singlet or triplet carbenes, since interconversion of the singlet and triplet state is improbable if the two electrons are in the same region of space[7] and do not move in the vicinity of perturbing atoms of large atomic number[8] or para magnetic ions.[9]

The two intermediates were distinguished by virtue of the radical nature of the linear intermediate. Because there was no relationship between the variations of rate with structure for the addition of $:CBr_2$ and radical $\cdot CCl_3$ to olefins, Skell concluded that (I) was not the intermediate in the olefin-dibromocarbene reaction. The fact that the $:CBr_2$ reaction was cis[10] stereospecific also weighted the rejection of (I).

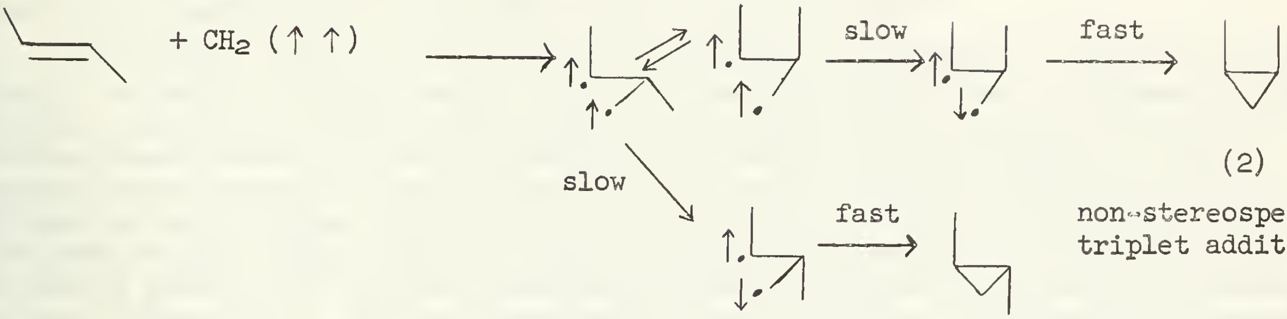
Correlation of relative rates of reaction with three-center type association reactions such as the epoxidation of olefins with peracetic and perbenzoic acids[11,12] and the bromination of olefins,[13] which involve a 2-electron deficient agent, show noteworthy resemblance.

Skell thus intuitively proposed that singlet carbenes add to olefins stereospecifically, since simultaneous bonding of the two olefinic carbons can take place. Unpaired spins precluding simultaneous bonding to the olefinic carbons, triplet carbenes add to olefins non-stereospecifically, since the formation of a linear intermediate allows rotation about the carbon-carbon single bonds. Nothing is said about the electronic state of the carbene when it is first formed. The equations

below summarize the Skell theory.



stereospecific
singlet addition (1)



(2)

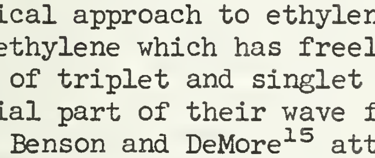
non-stereospecific
triplet addition

USE OF SKELL'S THEORY

Although Skell's unproved controversial hypothesis is intuitive and is perhaps an over-simplification of the spin state problem, its use and general acceptance have been widespread in the literature as an explanation for the outcome of methylene insertion and addition reactions. Many chemical means, not necessarily successful, have been conceived in an attempt to unequivocally demonstrate the validity of Skell's notion. Often the dividing line between use of theory to explain results and use of results to explain theory has been quite fine. The remainder of this seminar will deal with work which has been used to support Skell's hypothesis.

Although alternative theories which adequately account for the outcome of methylene reactions have been independently proposed by Hoffmann[14] and Benson and DeMore,[15] no chemical means so far have been published which have convincingly proved the correctness of one over the other or which have distinguished the different intermediates postulated in the various theories.

In extended Hückel calculations on the ground state trimethylene radical, $^{\cdot}CH_2CH_2CH_2^{\cdot}$, Hoffmann found that the topmost electrons occupy an orbital that is the antisymmetric combination of the terminal p orbitals. The Woodward-Hoffmann rules predict that a structure of this type would close to cyclopropane in a conrotatory manner and so preserve the original steric configuration. The first excited state of trimethylene has freely rotating methylene groups. Thus (from a correlation diagram) the $^1A_1$ state of $:CH_2$ in its approach to ethylene prefers an initial unsymmetrical approach correlating with ground state trimethylene with its large barrier to rotation. Collapse to ground state cyclopropane then occurs. Although the singlet and triplet B_1 states of methylene may prefer a symmetrical approach to ethylene, orbital symmetry forces correlation with the excited trimethylene which has freely rotating methylene groups. The difference in specificity of triplet and singlet methylene reactions is thus related to differences in the spatial part of their wave functions, rather than to spin difference.



Benson and DeMore[15] attribute non-stereospecificity to isomerization from excess vibrational and electrical energy. For a discussion of this theory see Kirmse.[2]

Gale and co-workers[16] have suggested that product differences arise from steric repulsions in the linear diradical intermediate.

Methylene has been found spectroscopically to decay from an initially formed singlet state to a more stable triplet (linear configuration[17]) ground state.[18] The amount of triplet formed is proportional to the pressure of an inert gas such as nitrogen. For a mathematical treatment for the conversion of singlet to triplet methylene, see Bader and Generosa.[19] The fact that chemical evidence from independent

sources is in agreement with spectroscopic and mathematical findings lends support to the idea that singlet and triplet intermediates are existent and that these different spin states provide criteria for explaining differences in reaction products.

Although it is generally accepted that free carbenes are involved in ketene and diazomethane decompositions in the gas phase, the concept of free divalent species as intermediates in the decomposition of diazo compounds in the condensed phase has recently come under attack.[20] The stereochemistry and spin states of carbenoids has already been discussed and will not be considered here.[21]

REACTIONS OF METHYLENE AND ITS DERIVATIVES IN THE GAS PHASE

The study of $:CH_2$ in the gas phase has been quite extensive. In order to establish Skell's method of distinguishing singlet and triplet spin states, an attempt was made to find a system in which a single carbene species exhibited both kinds of behavior. Diazomethane:2-butene mixtures photolytically reacted with and without nitrogen present as an inert gas have provided such a system. It was thought that collision of the initially formed singlet $:CH_2$ with the inert gas would cause deactivation to the more stable triplet $:CH_2$ which would subsequently react. With only small amounts of olefin present, collisional deactivation would occur before the carbene reacted in the singlet state. Several complications arise however. The dimethylcyclopropane initially formed from the addition of singlet $:CH_2$ to olefin contains enough kinetic energy[22] (ΔH_f of $:CH_2$ = 86 kcal/mole) to cause geometrical and structural isomerization. Thus the direct photolysis of diazomethane with cis-2-butene gives cis- and trans-1,2-dimethylcyclopropane, cis- and trans-2-pentene, 2-methyl-2-butene, 2-methyl-1-butene, and small amounts of ethylene from the attack of $:CH_2$ on diazomethane.[23,24]

Early work[25] with the olefin:methylene:nitrogen system was criticized by Frey[26] on the grounds that at the low pressures used (560 mm.) non-stereospecificity resulted from geometrical isomerization of excited cyclopropane instead of from triplet $:CH_2$ addition. Repeating Anet's work, Frey[26] used pressures of 2000 mm. to deactivate excited intermediates. Also nitrogen is 25% less efficient than 2-butene in deactivating excited dimethylcyclopropane. Although the addition of the triplet quencher oxygen brought about stereospecific addition of carbene to olefin under conditions favorable to triplet formation, DeMore and Benson questioned the original presence of triplet carbene. They felt that dilution with nitrogen in place of olefin led to decreased deactivation efficiency. Therefore, isomerization, not triplets, caused non-stereospecificity. The most definitive work is that of Bader and Generosa.[19] They photolyzed a mixture of diazomethane and cis-2-butene (in the constant ratio 2.5:1) in the presence of an increasing partial pressure (0 - 850 mm) of an inert gas. The yield of trans-1,2-dimethylcyclopropane (expressed as a percentage of total C_5 products) is high at low pressures of the inert gas due to the geometrical isomerization of the energized cis- isomer. As the pressure of inert gas is increased, the yield of trans isomer decreases, since there are now deactivating collisions with inert gas which prevent isomerization. As the pressure of inert gas is increased even further, the percentage of trans isomer starts to increase as there are now sufficient deactivating collisions to permit formation of triplet ground state $:CH_2$ before reaction with the olefin.

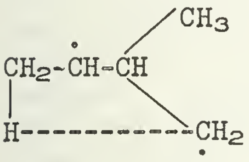
Photolysis of CH_2N_2 in the presence of increasing pressures of cis-2-butene with no inert gas yields decreasing amounts of the trans isomer. At high pressure the amount of trans isomer is still decreasing. This indicates deactivation by the cis-2-butene and inability of triplet formation before reaction. Thus the upswing of trans isomer formation at high pressures of inert gas indicates a second source of the trans isomer, i.e., formation of triplet carbene. Increase in amount of one isomer is accompanied by a decrease in amount of the other isomer.

The pressure at which trans isomer formation reaches a minimum is the point where triplet formation starts to become more important than geometric isomerization. Depending on the inert gas, this pressure is 100-250 mm. The fact that a minimum does exist disproves Benson and Demore's criticism of isomerization being the only reason for non-stereospecific addition.

Irradiation of a cis-2-butene:CH_2N_2:oxygen N_2 mixture at increasing pressures produces a curve in which at low pressures as much trans isomer is formed as in a

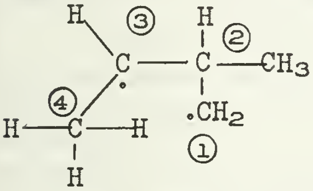
run without oxygen. As pressure is increased, the amount of trans isomer continues to decrease. Apparently collisional deactivation from the high pressure prevents geometrical isomerization while oxygen quenches the triplet carbene.

The fact that the percentage yield of 3-methyl-1-butene from cis-2-butene increases with increasing pressure of inert gas indicates that triplet $:CH_2$ is a precursor of this isomer. Insertion (a property of singlet $:CH_2$) is probably not the source of the isomer. Isomerization of energized cyclopropanes is not the major source, since the energy of the intermediate decreases with increasing pressure. The dependence of 3-methyl-1-butene on triplet methylene can be explained by proposing that the triplet adduct can not only close to give both cis- and trans-1,2-dimethylcyclopropane, but may undergo an internal hydrogen abstraction through a five membered cyclic intermediate (III) to give the 3-methyl-1-butene directly. The theory that triplet $:CH_2$ is involved in the formation of this isomer is strengthened by the fact that addition of oxygen to the system reduces the formation of the isomer to almost zero.


III

Sensitized reactions have been used to generate triplet methylene in the gas phase. Duncan and Cvetanovic̀[27] expected that in the triplet mercury (Hg 6^3P_1) photosensitized decomposition of ketene or diazomethane, triplet methylene would be formed because of spin angular momentum conservation. Methylene thus generated was allowed to react with cis- and trans-2-butene at 500 mm. and with isobutene at about 200 mm. In the case of the cis- and trans-2-butene, the product mixture ratios were within 4% of Frey's work,[23,24] thus indicating a similarity in methylene spin states for both workers. The non-stereospecific reaction, at least by Skell's hypothesis, indicates that triplet methylene was produced. Comparison of Cvetanovic̀'s sensitized diazomethane:isobutene reaction with Frey's direct photolysis shows quite different results. The fact that Cvetanovic̀ found a large increase in the amount of 1,1-dimethylcyclopropane with a corresponding reduction in the yields of insertion products indicates the triplet, which does not give random C-H insertion.

Like Skell, Cvetanovic̀ suggested the initial formation of a diradical triplet addition complex (IV), in which partial rotation around the original carbon-carbon double bond was responsible for the non-stereospecific formation of addition products. Since there was no evidence for random insertion of triplet methylene into C-H bonds, the olefinic C_5 products must have been formed by rearrangement in the diradical by H or CH_3 migration. For example, methyl migration from C^2 to C^1 or C^3 (1,2-shift of methyl, occurring perhaps partly or entirely externally) would give cis-trans-2-pentene and 3-methyl-1-butene, respectively.


IV

SUBSTITUTED METHYLENES

The amount of data available from the study of substituted methylene is abundant. Certainly Skell's theory should be applied to methylene derivative spin states with care, since rates of spin inversion can be expected to be greatly influenced by substitution.[28] Thus faster spin inversion rates should lead to higher concentrations of triplet methylenes.

Skell and Wescott[29] have recently made a study of dichlorocarbene in the gaseous state under vacuum. Until that time, all studies of the chemical properties of $:CCl_2$ were carried out in the condensed phase, where association of the carbene with solvent or other Lewis bases could occur. Miller and Whalen[30] have reported that $LiCCl_3$ in ether is thermally stable at -100° and yet reacts readily with cyclohexene to produce 7,7-dichloronorcarane. Thus, by analogy, it is possible that the properties which were reported were not those of the free carbene. By pyrolyzing $CHCl_3$ or CCl_4 (1500°) under high vacuum (10^{-4} mm.) where free flight from the generating source was required to encounter an olefinic reactant (cis- or trans-2-butene), $:CCl_2$ was generated in an apparently free state. Products were condensed on the cold (-196°) wall of the reaction vessel. Kinetic[31] and mass spectrometry[32] studies support the following decomposition reactions.

$CHCl_3 \rightarrow HCl + :CCl_2$ $CCl_4 \rightarrow Cl + \cdot CCl_3$ $\cdot CCl_3 \rightarrow Cl + :CCl_2$

Pyrolyses of both starting halides gave 83-86% C_2Cl_4, 14-17% of the cis cyclopropane and 14-16% of the trans cyclopropane from the cis and trans olefin, respectively. There was no formation of the "wrong" isomer in any run. C_2Cl_4 was considered the result of the following reactions:

$2:CCl_2 \rightarrow CCl_2{=}CCl_2$ $2\cdot CCl_3 \rightarrow CCl_3{-}CCl_3 \rightarrow Cl_2 + C_2Cl_4$

Of the possible neutral, one-carbon radicals which might be present in the pyrolysis zone, $:CCl_2$ seemed to be the most reasonable precursor of the dichlorocyclopropanes.

Skell's stereospecific additions agreed with those carried out in the condensed phase with $:CX_2$ from base and haloform.[33] Because of the stereospecificity of the reaction, Skell suggested that the uncomplexed dichlorocarbene intermediate must be in a singlet state, which was also probably the ground state. He justified the ground state designation by pointing out that there was no spin requirement for the decomposition of $\cdot CCl_3$ to $:CCl_2$ and Cl, so that, presumably, the more stable form would be produced. Also there were several routes for spin relaxation to the most stable spin state in the interior of the graphite chamber: a) collision with a doublet atom or molecule or free electrons (thermionic emission), b) collision with the graphite walls which, by virtue of conducting electron bands, should behave as a paramagnetic catalyst.

Mitsch[34] has studied the addition of difluorocarbene to olefins in the gas phase as a general, one-step route to difluorocyclopropane derivatives. Difluorocarbene, generated either by photolysis or pyrolysis of difluorodiazirine, added smoothly to olefins to form the corresponding difluorocyclopropane. The only side product with a 5-10 mole excess of olefin at 25-285° was tetrafluoroethylene. The reaction was found to be stereospecific (singlet carbene) with no trans isomer being formed in the photolytic reaction of cis-2-butene. Mitsch suggested that since even a large excess of olefin and high temperatures did not prevent the formation of tetrafluoroethylene, a large number of collisions were ineffective, thus indicating reactions of ground-state difluorocarbene. This suggestion, however, does not consider the formation of tetrafluoroethylene from attack of the carbene on the difluorocyclopropane.

REACTIONS OF METHYLENE AND ITS DERIVATIVES IN SOLUTION

Chemical evidence for the decay mechanism of methylene is difficult to obtain in gas phase reactions, because the product formed by addition of singlet methylene to an olefin is a hot cyclopropane that can isomerize if it is not deactivated rapidly.[21,26,35] In solutions, however, reaction of $:CH_2$ with the olefin is usually so rapid that singlet to triplet decay mechanisms do not have time to occur by collision-induced inter-system crossing.[36] Thus most methylene additions in the condensed phase have been random with alkane carbon-hydrogen bonds,[37] have shown little radical character, and have been stereospecific, criteria for the singlet spin state.

Hammond and co-workers[38] found that direct photolysis of the 2-butenes and diazomethane in octane produced the stereospecific addition products and the expected insertion reactions as reported by other workers.[10,26,39,40] When the decomposition was photosensitized with benzophenone, cis-2-butene produced cis- and trans-1,2-dimethylcyclopropane in a 2:1 ratio, plus a small amount of another non-olefinic compound. Photosensitized decomposition in the presence of trans-2-butene gave trans-1,2-dimethylcyclopropane, a small amount of cis-1,2-dimethylcyclopropane, and a trace of an olefinic compound. The non-stereospecific reaction is that which Skell predicts for triplet methylene. It is interesting to note that the photosensitized trans reaction gave only a small amount of the cis product. Apparently in some cases spin inversion must be a very fast process in solution, or there is steric hinderance.

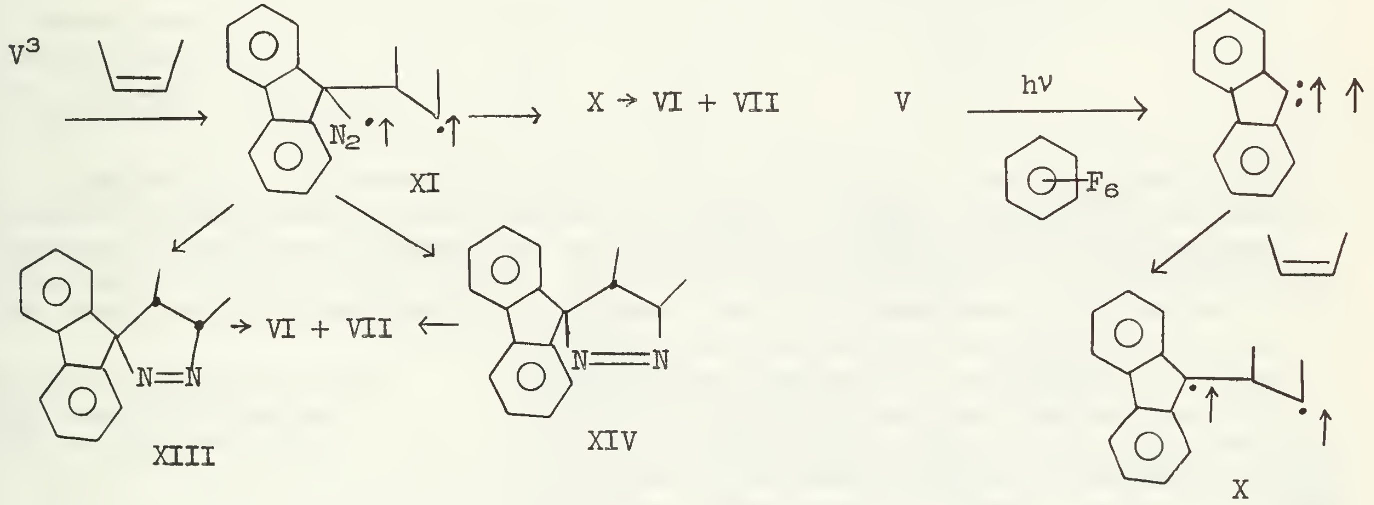
Hammond unsuccessfully tried to catalyze singlet-triplet interconversion[41] of methylene with the heavy atoms iron and iodine. Most likely $:CH_2$ reacts on nearly every collision with a substrate atom and the probability of its formation near an iron atom, at the concentrations used, was quite low.

Jones and Rettig[42] studied the addition of fluorenylidene (triplet ground state[43]) to various olefins by photodecomposition. They found that addition of the inert solvent,

hexafluorobenzene, decreased the stereospecificity of the addition. Thus irradiation of a solution of 9-diazofluorene (V) in *cis*-2-butene yielded *cis*- and *trans*-2,3-dimethylspiro [cyclopropane-1,9'-fluorene][44] (VI, VII) in the ratio 1.95. Irradiation in *trans*-2-butene gave the same two products in the ratio 0.06. Similarly, addition of the carbene to *cis*-4-methyl-2-pentene gave *cis*- and *trans*-2-methyl-3-isopropylspiro [cyclopropane-1,9'-fluorene] (VIII, IX) in the ratio 1.21. Irradiation in the *trans*- isomer gave the *trans* product with only traces of the *cis*. The ratio of VI:VII smoothly decreased from 1.95 to .3 as hexafluorobenzene was added to the *cis*-2-butene reaction. With hexafluorobenzene VIII:IX decreased from 1.21 to 0.2.

The authors proposed that the addition of the inert solvent results in increased intersystem crossing from singlet fluorenylidene to the more stable triplet[43] by non-reactive collisions. The resulting triplet carbene would then be expected to add non-stereospecifically according to the Skell theory. Benson and DeMore[15] have suggested that the less reactive, more selective carbenes (not necessarily in the triplet state) are responsible for all non-stereospecific additions. Assuming that the more selective carbenes go through a diradical intermediate, one postulates that the rotational barrier of the diradical must be lower than the closure barrier. The recent work of Hammond[38] discussed above, and the work of Closs[45] indicate that closure can be faster than rotation in solutions. *Trans*-2-butene gave only 12% of the *cis* adduct (VI) when large amounts of the fluorocarbon were present--conditions that would give low energy fluorenylidene. Here, rotation was slow compared to closure. The *cis* olefins gave products which had isomerized considerably, which could be explained on either the basis of excess energy causing isomerization (Benson and DeMore) or on the basis of reaction triplets. The lack of much scrambling for the *trans* case, however, seems to support the formation of triplets.

Triplet V could be responsible for some or all of the non-stereospecific addition observed. Several researchers[46,47] have reported that some carbene precursors undergo intersystem crossing before decomposing to carbenes. If the rate of loss of nitrogen from XI was faster than the rate of closure, the resulting diradical X would be the same as postulated in the triplet carbene mechanism. However, XI could close to give a pyrazoline faster than it loses nitrogen. Since pyrazolines are known to decompose upon irradiation in a stereospecific manner,[48] it is possible that rotation occurs in XI at a rate faster than closure to form XII and XIII. Decomposition of these two pyrazolines would give overall non-stereospecific addition.

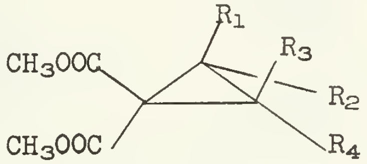


The addition of the triplet quencher 1,3-butadiene to the fluorenylidene-*cis*-2-butene system increased the stereospecificity of the reaction and gave products VI and VII plus the diene addition product, 2-vinylspiro[cyclopropane-1,9'-fluorene]. As more 1,3-butadiene was added, the ratio of VI to VII increased and the ratio of butene adducts to diene adducts (VI + VII/XIV) decreased. It seems reasonable that a species adding to give a diradical would be better able to take advantage of allylic resonance than a species adding in a one-step process to give cyclopropane

directly. The addition of hexafluorobenzene with the diene to a constant ratio of *cis*-2-butene to 1,3-butadiene decreased the ratio of VI to VII, since more triplets were formed.

Oxygen had an effect similar to the diene.

In similar experiments, Jones and co-workers,[49] in an attempt to observe intersystem crossing from the initially produced singlet to the presumably more stable triplet, studied the decomposition of diazomalonic ester in the presence of *cis* olefins as a function of added inert medium. With hexafluorobenzene as the inert solvent, the benzophenone photosensitized decomposition of diazomalonic ester yielded *cis*- and *trans*-cyclopropane derivatives from the *cis* olefin, thus implying that the triplet state did add non-stereospecifically. Table 1 gives the overall results.



A $R_1 = R_3 = H$ $R_2 = CH_3$ $R_4 = CH(CH_3)_2$

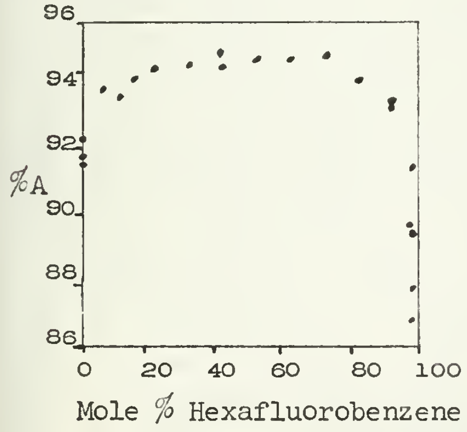
B $R_1 = R_4 = H$ $R_2 = CH_3$ $R_3 = CH(CH_3)_2$

Table 1. Irradiation of Methyldiazomalonate in *cis*-4-Methyl-2-pentene

Conditions	%A	%B	Total Yield of Cyclopropanes
$(CH_3OOC)_2CN_2 + h\nu$	92	8	39.8
$(CH_3OOC)_2CN_2 + Ph_2CO + h\nu$	15	85	43

Apparently, intersystem crossing is rather difficult, since large amounts of hexafluorobenzene must be added before the amount of *trans* cyclopropane derivative increases. As figure 1 shows, the amount of *cis*-cyclopropane actually increases when inert solvent is first added. Only after a broad maximum at around 50% does the amount of *cis* isomer begin to decrease. This is interpreted by Jones as indicating two sources of the *trans* product, each dependent upon moderator concentration in a different way. *Cis*-2-butene gave similar results, with no solvent olefin isomerization under reaction conditions. The final decline in the amount of *cis* product is interpreted as being a result of triplet carbene.

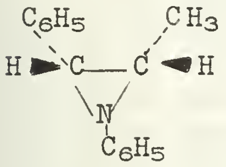
Figure 1. Reaction with *cis*-4-Methyl-2-pentene and Hexafluorobenzene

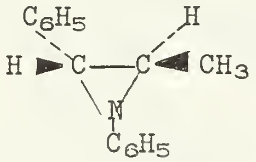


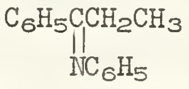
The observed initial increase of *cis* isomer might be explained in two ways. First, excited diazo compound, before it decomposed, could add to the olefin to form a pyrazoline. Lack of stereospecificity in the formation process would give *trans*-cyclopropane. The added inert solvent would give the excited diazo compound more time to lose nitrogen, thus decreasing the amount of *trans*-cyclopropane from this process. Second, Hoffmann[50] calculates that the first excited singlet state of methylene should add in a non-stereospecific manner to olefins. If a similar intermediate is produced

during the irradiation of dimethyldiazomalonate, the added hexafluorobenzene would increase the amount of deactivation to the lowest singlet state, which should add to olefins stereospecifically.

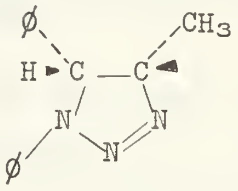
One of the key assumptions in Skell's theory is that sigma bond rotation is faster than spin inversion in 1,3-diradicals. Since it is not known whether additions of singlet carbene to olefin involve 1,3-diradical intermediates, comparison of triplet and singlet diradicals is uncertain. Scheiner[51] reported the generation of such radicals by a non-carbene path. Different mixtures of the same three products, *cis*-aziridine XVI,[52] *trans*-aziridine XVII[52] and propiophenone anil XVIII were produced from the direct irradiation of solutions of triazolines XIV and XV.

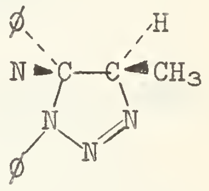

XVI


XVII


$C_6H_5\underset{\substack{\| \\ NC_6H_5}}{C}CH_2CH_3$

XVIII


XIV


XV

66

Direct photodecomposition of XIV gave 65% XVI, 17% XVII, 18% XVIII, while XV gave 22% XVI, 16% XVII, 12% XVIII. In the benzophenone-sensitized photodecomposition XIV gave 60% XVI, 36% XVII and 4% XVIII while XV gave 54% XVI, 42% XVII and 4% XVIII.

There was no *cis-trans* triazoline interconversion, and the products were photostable under the conditions employed. The same product distributions described in the preceding paragraph were observed when oxygen was excluded from the system or when 4.9 M piperylene was present in the system. Also quantum yields of nitrogen evolved from XIV and XV were unaffected by oxygen. Since the reaction is predominantly stereospecific, even in the presence of triplet quenchers, the intermediate involved is an excited singlet state, and ring closure to the aziridine occurs more rapidly than bond rotation. Photo- and thermal decomposition of 1-pyrazolines has previously been reported to be stereospecific.[48] When the same reaction was carried out with the sensitizer benzophenone, no new products were detected.

The excited triplet triazoline loses a singlet[53] nitrogen to give a triplet 1,3-diradical, a species which must undergo spin inversion before closure to aziridine.[54] Direct photolysis shows that ring closure is rapid for a singlet diradical. Therefore loss of stereospecificity indicates that spin inversion is slower than bond rotation. Scheiner suggests that equilibrium of the triplet rotamers is closely approached since product composition from each isomer in the sensitized photodecomposition is similar. By way of comparison, Ciganek,[55] in working with the $:C(CN)_2$-2-butene system diluted with cyclohexane, found that the equilibrium concentration of rotamers derived from dicyano-carbene was 30:70 (*cis*:*trans*).

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ANODIC OXIDATION OF AMINES AND AMIDES

Reported by William D. Shermer October 16, 1967

INTRODUCTION

Research in the anodic oxidation of amines and amides has been primarily devoted to the use of electrochemistry as an analytical tool and it has been only recently that any detailed studies of the mechanism of these reactions have been carried out. This seminar will discuss these mechanisms and show correlations between the anodic oxidation and other chemical oxidations of amines and amides. The chemical oxidations will not be covered in complete detail and a full review of these reactions is not intended. The anodic oxidation of nitrogen heterocycles will not be included in this seminar.

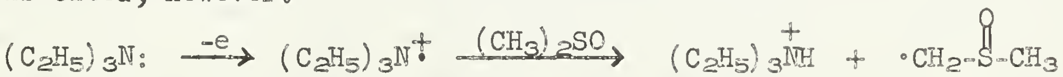
AMINES

In 1956, Streuli and his coworkers[1,2] studied the coulometric titration of aliphatic and aromatic amines and developed quantitative analytical techniques using solutions of the amines in acetonitrile with lithium perchlorate trihydrate as the supporting electrolyte. (The solvent for all electrolytic experiments described in the seminar was acetonitrile and the anode was a platinum electrode unless otherwise stated.) The principle product identified was hydrogen ion; its production was attributed to the water introduced by the electrolyte. However, hydrogen ion was generated even under anhydrous conditions and this led Schmidt and Noack[3] and Billon[4] to believe that it arose from the background reactions of the solvent with perchlorate radicals generated during the oxidation. Both Maki and Geske[5] and Billon have reported esr spectral evidence for an intermediate which they believed to be the perchlorate radical but which was later identified as the chlorine dioxide radical.[6] In 1963, Russell[6] examined the oxidation of triethylamine in acetonitrile with perchlorate as the supporting electrolyte. Without the amine present, Russell could follow the destruction of perchlorate at the anode gravimetrically by removing aliquots and precipitating the perchlorate with methylene blue, indicating initial production of perchlorate radical which could be further oxidized to a chlorine dioxide radical when the trapping agent is not present. However, when triethylamine was present, the destruction of perchlorate was completely inhibited and a well-defined irreversible anodic chronopotentiometric wave for the amine was produced. To account for the reaction of triethylamine Russell proposed the reactions given in Equation 1. The cyanomethyl radical could couple head to head to form succinonitrile,

(1) $$(C_2H_5)_3N \longrightarrow (C_2H_5)_3N^{+\cdot} + e \xrightarrow{CH_3CN} (C_2H_5)_3\overset{+}{N}H + \cdot CH_2CN$$

observed by Schmidt and Noack, or head to tail to form N-cyanomethylketenimine, observed by Eberson,[7] along with succinonitrile, in his studies of the electrolysis of α-cyanoacids.

Dapo and Mann[8] studied the oxidation of triethylamine using dimethylsulfoxide and lead (II) nitrate as the supporting electrolyte. Coulometric analysis indicates that 1.02 ± 0.04 electrons/molecule are involved in the reaction. By showing that the product of the current density (i_o) and the square root of the transition time (τ- the time at which the concentration of the electrolyzed species is equal to zero at the electrode surface) was a constant over a ten-fold range in i_o, Dapo and Mann demonstrated that the reaction was diffusion controlled and not subject to kinetic complications prior to the electrode reaction. Triethylammonium salts were a principle reaction product and, to account for their production, the reaction sequence shown in Equation 2 was proposed. No evidence for the dimethylsulfoxide radical is cited, however.

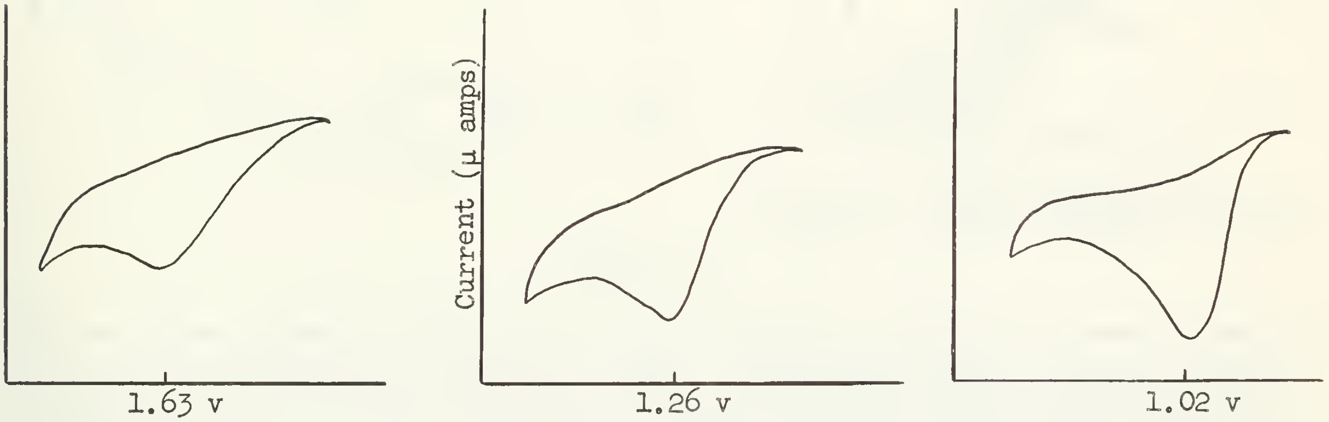
(2)


$$(C_2H_5)_3N\!: \xrightarrow{-e} (C_2H_5)_3N^{+\cdot} \xrightarrow{(CH_3)_2SO} (C_2H_5)_3\overset{+}{N}H + \cdot CH_2\text{-}\overset{O}{\overset{\|}{S}}\text{-}CH_3$$

Current reversal chronopotentiograms gave a reverse transition time of zero, indicating that the over-all reaction is irreversible. Using the criteria developed by Reinmuth[9] for mechanistic interpretation of electrolytic reactions, Dapo and Mann

state that the charge transfer is reversible and is followed by an irreversible chemical reaction.

Cyclic voltammetry curves of 19 aliphatic amines studied by Mann[10-12] showed an irreversible oxidation, contradicting the conclusion of Dapo and Mann. Three representative curves are shown in Figure 1. The lower portion of the curve represents the anodic portion of the cycle, i.e., the oxidation of all the reduced species in the vicinity of the electrode, and the upper portion of the curve represents the cathodic half of the cycle, the reduction of the oxidized species in the vicinity of the electrode. The order of increasing difficulty of oxidation, as shown by the increases of potential, was tertiary < secondary < primary amines. Hydrogen atom is more strongly electron withdrawing than an aliphatic group and, therefore, replacing alkyl groups with hydrogens should make an electron less available and require an increase in potential to affect its removal. A good correlation of polarographic half-wave potentials with Hammett-Taft polar substituent constants was demonstrated. The graph which they obtained is shown in Figure 2. Rigorous agreement, however, can only be expected for reversible electrode reactions. For irreversible reactions, a correlation can be obtained only if the transfer coefficients (β) for all members of the group are the same or nearly the same. β is the transfer coefficient for an irreversible reaction and is defined as the fraction of the electrode potential which favors the reaction. For secondary and tertiary amines, βn_a ranges from 0.22 to 0.34 and should be comparable. (n_a is the number of electrons transferred in the rate controlling step per molecule of reactant.) However, βn_a for primary amines ranges from 0.12 to 0.18 and, thus, the primary amines will constitute a separate group. With secondary or tertiary amines, as small an alteration as the change from a methyl group to an ethyl group causes the oxidation to take place at a noticeably lower potential. With primary amines, a change from a methyl group to a t-butyl group has no effect. No explanation for this has, as yet, been proposed.



n-propylamine
9.44 v/sec; 0.2 sec

← Potential (volts)
Di-n-propylamine
10.14 v/sec; 0.2 sec

Tri-n-propylamine
11.08 v/sec; 0.2 sec

Figure 1

In an effort to elucidate the detail of the mechanism, Barnes and Mann[13] studied the oxidation of primary aliphatic amines, combining controlled-potential coulometry with cyclic voltammetry. After oxidation, the following products were identified: salts of the protonated starting amine, ammonium salts, aldehydes with the same carbon skeleton as the starting amine, hydrocarbons, and nitrogen.

In controlled-potential electrolysis without complications, the current decays exponentially with time as in as first order rate reaction. However, a curve was obtained for all of the primary amines tested, with the exception of t-butylamine, which passed through a minimum, increased, and then decayed again. This shape results from a delayed production of an electroreactive material in a sequence of reaction steps (See Figure 2). For ammonia and t-butylamine no peaks resulted and continuous decay to background was observed. However, a plot of log i vs time gave a curve

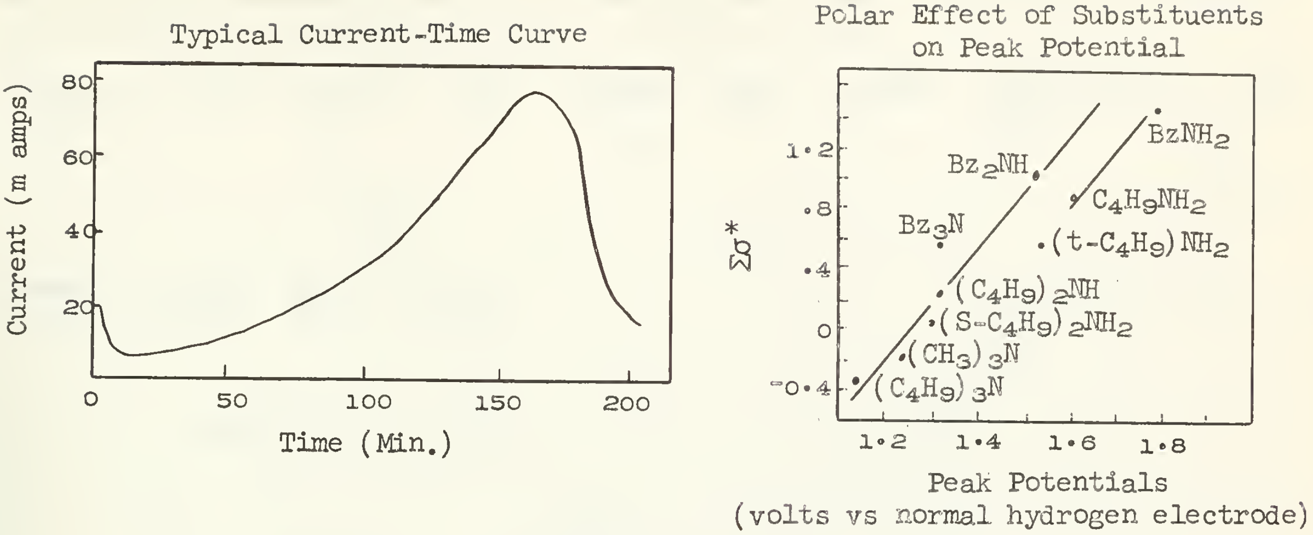


Figure 2

with two linear segments rather than one straight line. Electron counts varied from 0.71 to 0.81 electrons per molecule of amine. These nonintegral electron counts indicate that some starting material is being consumed by a chemical reaction with a product of the electrolytic oxidation to produce a nonelectroreactive species.[14]

Cyclic voltammetry curve slopes reflect rates of electron transfer when they result from a single, irreversible step. Assuming a single step, all tertiary and secondary amines show similar rates while primary amines show much slower rates. In all cases, the initial step is removal of an electron from the nitrogen atom. A long drawn out slope of the cyclic votammetry curve for primary amines would result if the mechanism consisted of two or more electron transfer steps, separated by a chemical step. This would require that steps 1 and 3 occur at about the same potential and

$$(3) \qquad A \xrightarrow[1]{-e} B \xrightarrow[2]{} C \xrightarrow[3]{-e} D$$

that step 2 was rate-controlling but, also, fast enough to produce significant concentrations of C within 0.1 sec. (time of one cycle was 0.2 sec.). The observed differences in curve shape for the various classes of amines do not necessarily imply drastic differences in reaction mechanism but could arise simply from differences in the rates of step 2.

The mechanism shown in Equation 4 is of the type necessary to generate the current-time curve in Figure 1. In this sequence, step 4 is a slow chemical reaction requiring many minutes to generate component E. Equations 3 and 4 cannot contain the

$$(4) \qquad A \xrightarrow[1]{-e} B \xrightarrow[4]{\text{slow}} E \xrightarrow[5]{-e} F$$

same steps because of the difference between the time factors involved in steps 2 and 4. To fulfill the need for different chemical rates, Barnes and Mann proposed the mechanism shown in Figure 3 involving two competing reactions. The intermediate III could be represented by any of several resonance structures. Path A corresponds to Equation 3 and path B, to Equation 4.

The course of electrolysis can be followed by UV and, at a period of time corresponding to the rising portion of the current-time curve, a peak appears at 256 mμ which cannot be identified as starting material or as a product. Hammond and coworkers[15] observed a peak at the same wavelength in their studies on ion-pair formation in the reaction of alkyl iodides with silver salts. They attributed the peak to attack by a carbonium ion on the nitrogen of the nitrile group of the solvent, acetonitrile, followed by condensation of the resulting ion to a polymer. Eberson and Nyberg[16] have reported reactions of electrochemically generated carbonium ions

with acetonitrile providing support for path B of the mechanism below. If the UV peak at 256 mμ observed by Barnes and Mann is due to the reactions of a carbonium ion, this would be supporting evidence for step 11 below.

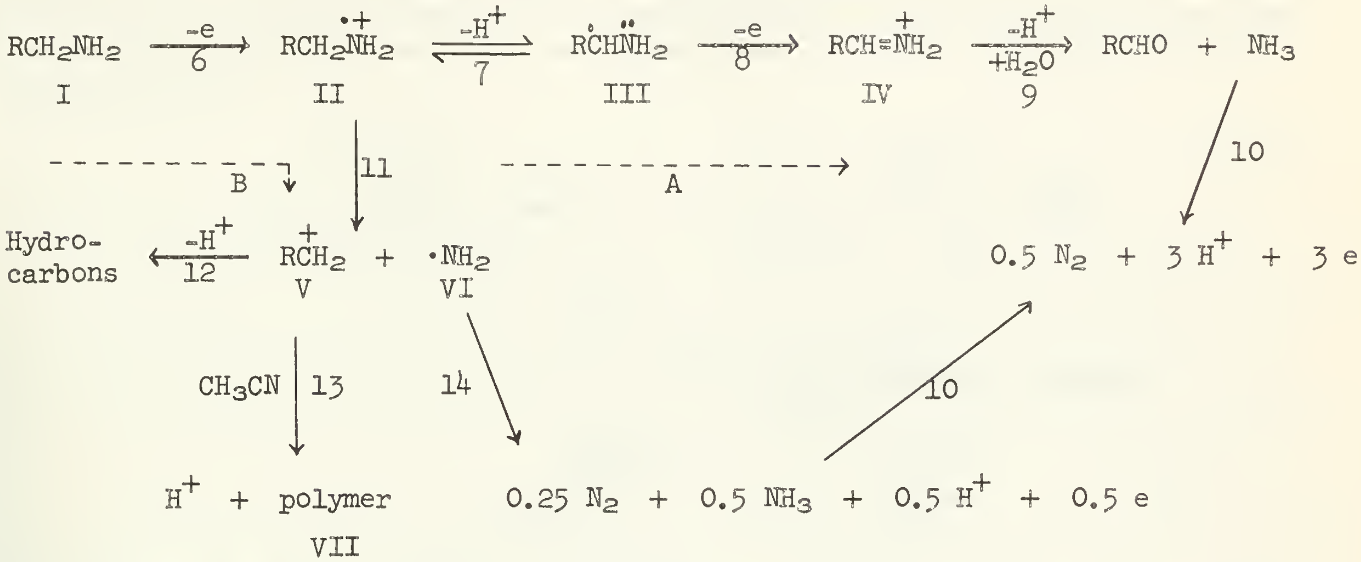

RCH_2NH_2
I
-e
6
$R\dot{C}H_2\overset{\bullet +}{N}H_2$
II
$-H^+$
7
$R\dot{C}H\ddot{N}H_2$
III
-e
8
$RCH{=}\overset{+}{N}H_2$
IV
$-H^+$
$+H_2O$
9
RCHO + NH_3
10
B
11
A
Hydro-carbons
$-H^+$
12
$R\overset{+}{C}H_2$ + $\cdot NH_2$
V
VI
$0.5\ N_2 + 3\ H^+ + 3\ e$
CH_3CN
13
14
10
H^+ + polymer
VII
$0.25\ N_2 + 0.5\ NH_3 + 0.5\ H^+ + 0.5\ e$

Figure 3

Sparging the sample cell during the electrolysis of an amine eliminates the characteristic peak from the current-time curve. Since ammonia, which does react at the potential in question to produce nitrogen and protons, would be removed by sparging, Barnes and Mann suggest, in support of step 10 in their proposed mechanism, that ammonia is the reactive species producing that peak. However, reaction 14 of their proposed mechanism should also produce current and, therefore, either the ammonia alone does not produce this peak or reaction 14 does not occur. An alternative to reaction 14 which would be a chemical reaction and, thus, would not contribute to the current is given in Equation 5. Secondary and tertiary amines do not show the peak in the current-time curve when oxidized at low potential. While all amines could undergo the reactions analogous to steps 6, 11, 12, and 13, only the primary amines will give a precursor to ammonia.

$$6\ \cdot NH_2 \longrightarrow N_2 + 4\ NH_3 \tag{5}$$

The controlled-potential coulometry was carried out at about 1.2 volts and would proceed principally by way of path B, with path A contributing to only a small extent. With the cyclic voltammetry, however, potentials as high as 1.9 v are reached in each cycle. The higher potential would increase the rate of reaction 8 without affecting the rate of the slow chemical step 11. Thus, if the rate of equilibrium of step 7 is rapid compared to the rate of step 11, path A would predominate and the observed cyclic voltammetry curve would result.

The cyclic voltammetry experiments discussed by Mann and coworkers covers only a narrow range of sweep rates. They state that the slope of the voltammetry curve decreases as the sweep rate is increased from 10 to 20 volts per second. This may be an indication that a very rapid sweep rate may isolate the peak for only the first reaction by forcing the first electrolytic step to occur more rapidly than the chemical equilibrium of step 7. This would eliminate any significant contribution of step 9 to the voltammetry curve by not allowing a sufficient build up of concentration of compound III for the second electrolytic step to become important. This may resolve the question of reversibility of the first electrochemical step. By going to a very slow sweep rate, one might be able to observe two peaks, provided the second electron transfer occurs at a higher potential and is sufficiently separated from the potential of the first transfer.

The structure of t-butylamine prevents that compound from producing aldehydes, i.e., from proceeding by path A. Therefore, it must go exclusively by way of path B to give t-butyl alcohol and isobutylene - the most predominant hydrocarbon observed

for this amine. The mechanism would then predict a steep voltammetry curve and a current-time curve similar to that of other primary amines. Actually, a normal voltammetry curve and a current-time curve which decays to background with no peaks developing was produced. This could be accounted for if the rate-controlling step 11 is much faster than normal, the rate being enhanced by the stability of the t-butylcarbonium ion.

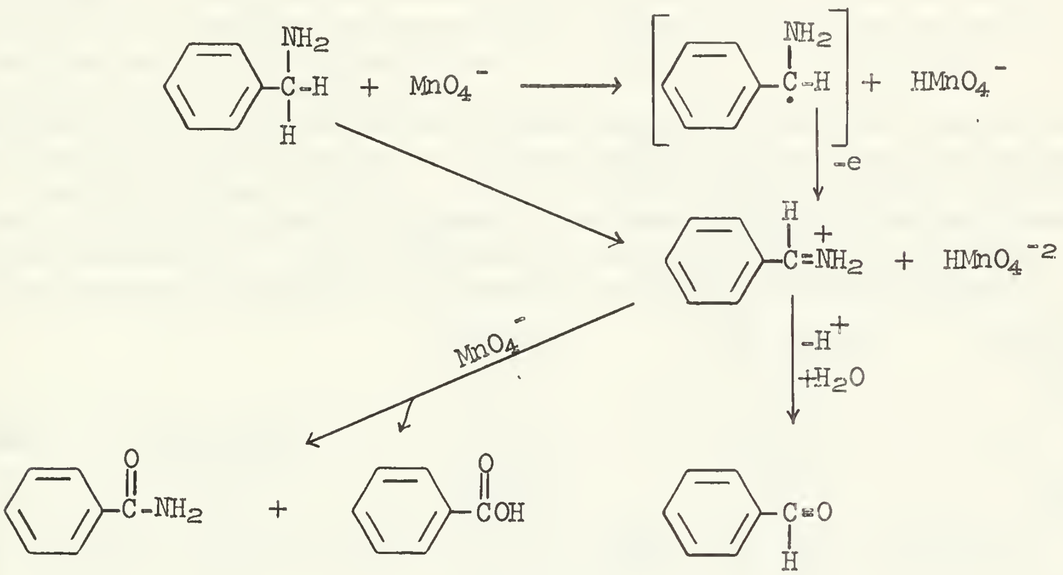
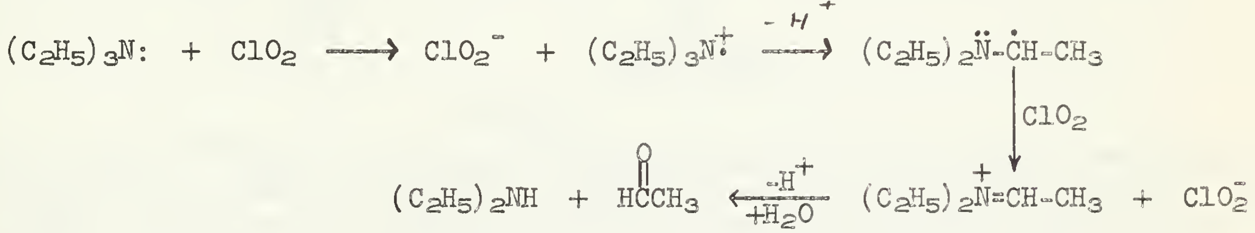


Figure 4

Path A of the mechanism proposed by Barnes and Mann can be compared to the mechanism, shown in Figure 4, suggested by Wei and Stewart[17] for the oxidation of primary amines by alkaline permanganate. Wei and Stewart postulated an ionic transition state with extensive charge separation resulting from the transfer of either electrons or hydride ions.

Rosenblatt and coworkers[18-20] studied the oxidation of triethylamine with chlorine dioxide to produce acetaldehyde and diethylamine. Two mechanisms were proposed: a) electron abstraction from the nitrogen atom (shown in Figure 5) and b) hydrogen abstraction from the α-carbon. For benzyldimethylamine at pH 9, the ratio of formaldehyde to benzaldehyde produced by the chlorine dioxide oxidation is almost 6 to 1 indicating nonselective dealkylation. Rosenblatt and coworkers believe that, if mechanism b was the predominant mechanism, benzaldehyde should have been the principle product and, on this basis, they state that mechanism a is the most likely. However, at pH 6.4, the ratio of aldehyde products is approximately 1 to 1 - showing selective dealkylation. Consequently, this is not a sufficient criteria to enable one to distinguish between the two mechanisms.



$$\begin{tikzcd}
(C_2H_5)_3N: + ClO_2 \arrow[r] & ClO_2^- + (C_2H_5)_3N^{+\cdot} \arrow[r, "-H^+"] & (C_2H_5)_2\ddot{N}-\dot{C}H-CH_3 \arrow[d, "ClO_2"] \\
 & (C_2H_5)_2NH + H\overset{O}{\overset{\|}{C}}CH_3 & (C_2H_5)_2\overset{+}{N}=CH-CH_3 + ClO_2^- \arrow[l, "-H^+"', "+H_2O"]
\end{tikzcd}$$

Figure 5

The deamination of primary amines by nitrous acid is somewhat similar to path B of the Barnes and Mann mechanism in that the decomposition of the diazonium salt yields a carbonium ion having the same carbon skeleton as the original amine and producing similar products.

The anodic oxidation of N-methylaniline and N,N-dimethylaniline in aqueous solution have been studied extensively by Adams and coworkers[21] as representative of the class of aromatic amines. Above pH 8, N-methylaniline shows two waves in its chronopotentiogram and only one wave below that pH; for N,N-dimethylaniline, the

two waves appear above pH 3; aniline shows only one wave throughout the whole pH range. If the two waves represented a stepwise oxidation involving the same number of electrons, the second step should be three times the height of the first. The first step represents the oxidation of species one in the vicinity of the electrode; the second step shows the oxidation of species two and that amount of species one which has diffused in to replace that previously oxidized. The fact that the transition time for step two is three times that of step one was derived by Delahay and coworkers[22] and verified experimentally by them. This is not observed for the aniline derivatives which indicates that the primary electrode process is probably followed by a chemical transformation.

The product of the oxidation of N,N-dimethylaniline has been identified as tetramethylbenzidine (XII), which is in turn oxidized under the reaction conditions to yield a quinone diimine (XIII). Two alternative charge transfer processes can be postulated. The first, shown in Figure 6, involves a single electron transfer to give the radical ion XI. This intermediate can then couple with a similar radical ion to give tetramethylbenzidine. The second mechanism, shown in Figure 7, involves a two electron transfer to form intermediate XIV which can then react with a molecule of unoxidized N,N-dimethylaniline.

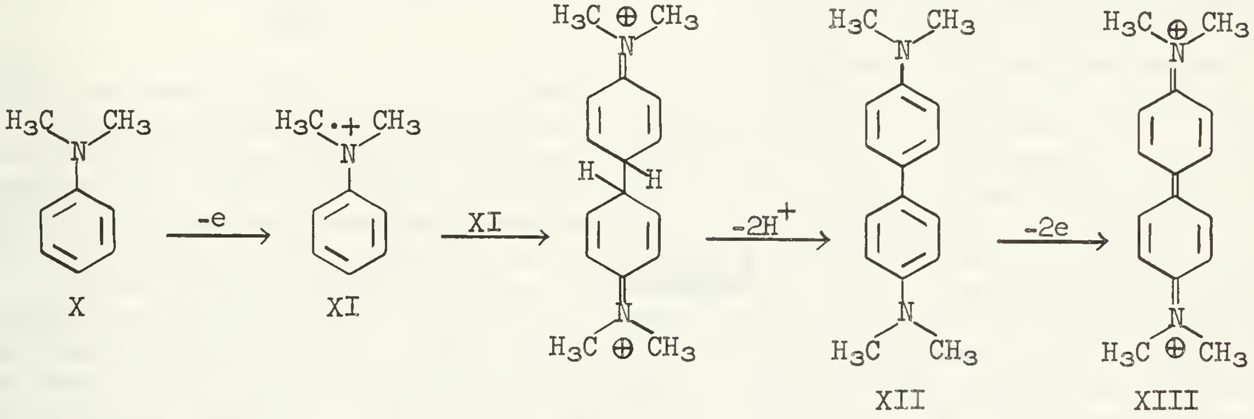


Figure 6

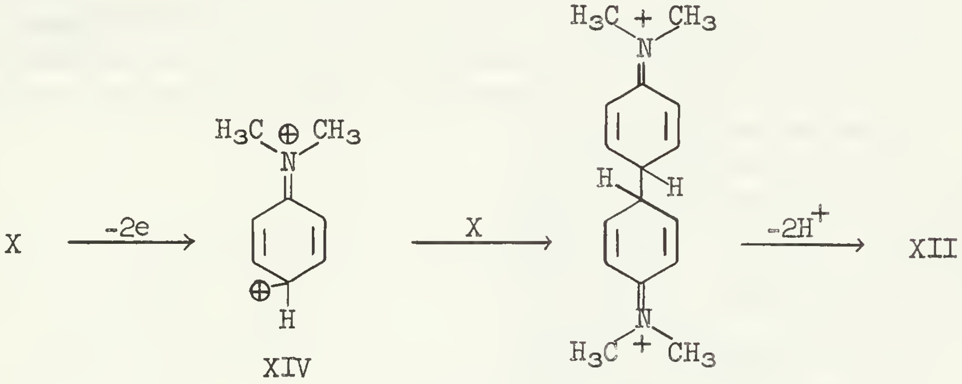


Figure 7

A Tafel plot,[23-25] which is a graph of log current vs potential under conditions of very rapid mass transport so that the electron process is rate controlling, will give a straight line whose slope equals βn_a and for N,N-dimethylaniline the slope was 1.23 indicating that, since β is less than one, n_a is two or larger. Another form of the Tafel plot is a graph of log current vs log concentration of X under similar experimental conditions as above. The slope of the straight line obtained from this graph indicates the molecularity of the reaction and, for N,N-dimethylaniline, the slope was 1.1. These results indicate that the first step involves a two electron transfer from one molecule of N,N-dimethylaniline.

Cyclic voltammetry curves of N,N-dimethylaniline were obtained using both platinum and carbon paste electrodes. The voltammetry curves obtained using the platinum electrode showed an initial irreversible reaction at 0.6 v vs the standard calomel electrode followed by the development of a reversible redox system at 0.45 v.

[illegible]

[illegible]

[illegible]

The reversible system is identical to that obtained with tetramethylbenzidine. The carbon paste electrode gave the same voltammetry curve below pH 4 but at higher pH's a second reversible redox system appears at 0.2 v. This second system is seen to increase with time at the expense of the other peaks, and has been shown to be a secondary reaction product resulting from the reaction of the oxidized tetramethylbenzidine and excess starting material. When XIII was prepared chemically, isolated as the perchlorate, and examined by cyclic voltammetry (below the potential at which N,N-dimethylaniline is oxidized), only the redox system at 0.45 v was observed. When N,N-dimethylaniline was added both reversible systems were observed. The solution of XIII developed a green color during the cyclic voltammetry studies and this color has been connected with the tetramethylbenzidine radical ion (~~[illegible]~~) by Naylor and Saunders[26] in their studies of dimethylaniline oxidation by peroxidase. Galus and Adams propose that the secondary reaction is the coupling of this radical ion with X. Experiments with N,N-dimethylaniline labeled in the para position with tritium show that the reaction involves the para position of the aniline compound. No structure was proposed but the compound shown in Figure 8 would be a possible product.

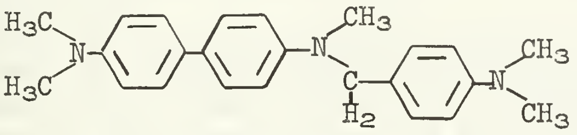
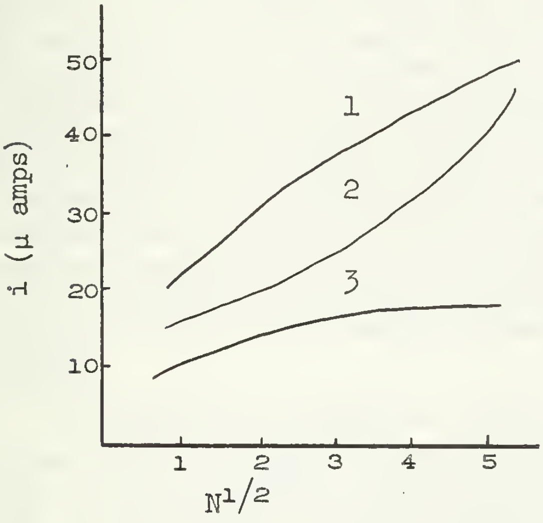


Figure 8

The scan rates used by Adams and coworkers were relatively slow, 1.94 volts per minute being the most rapid. If the charge transfer step is reversible and if the rate of the reverse reaction is slow compared to the rate of reaction of the dication, XIV, with N,N-dimethylaniline, the charge transfer could appear irreversible at the slow scan rates used. Further work is necessary to resolve this question.

If the charge transfer process is preceded ~~proceeded~~ by a slow chemical step, $i_p/V^{1/2}$ should vary with the scan rate V at constant electrode area, pH, and N,N-dimethylaniline concentration.[27] If previous chemical steps are absent or too rapid to be detected by this means, $i_p/V^{1/2}$ is independent of $V^{1/2}$. At carbon paste electrodes, i_p increased linearly with $V^{1/2}$ in the range of 0.096 to 1.94 v/min. and, hence, $i_p/V^{1/2}$ is a constant. Using the equation $(E_p - E_{p/2})_{Irr.} = 1.85 \frac{RT}{\beta n_a F}$, βn_a had a mean value of 1.06 which again indicates an initial charge transfer of two electrons. The equation was derived by Matzuda and Ayabe[28] and relates the peak potential and half-peak potential with the transfer coefficient. $E_p - E_{p/2}$ is related to the slope of the peak elongation ~~program~~ and, for an irreversible system, this is a constant.

Rotated double-disk electrode experiments provide supporting evidence for the reaction sequence proposed by Adams and coworkers. Figure 9 shows the variation of current with the number of revolutions/second (N) of the electrode. Curve 1 shows the current at the inner disk when a potential of 0.85 v is applied to the inner disk. Curve 3 shows the current at the outer disk when the potential at the outer disk is 0.6 v, insufficient to oxidize N,N-dimethylaniline, and the potential at the inner disk is 0.0 v, i.e., open circuit. Curve 2 shows the current at the outer disk when 0.85 v is applied to the inner disk and 0.6 v is applied to the outer disk. The rapid increase in slope of curve 2 is readily interpreted. At low rotation speeds, only a small amount of tetramethylbenzidine is swept out to the outer ring but is oxidized principally at the inner electrode. At higher rotation velocities, the rate of mass transfer becomes competitive with the rate of oxidation and a significant amount of XII reaches the outer electrode to be oxidized there.



A Plot of i vs $N^{1/2}$

Figure 9

Starting with generally tritium labeled N,N-dimethylaniline, Adams and coworkers[29] measured the radioactivity remaining in the nonvolatile products, which they presumed to be only the oxidized tetramethylbenzidine, from which they could calculate the number of moles of starting material fixed in the product. Then, by means of Faraday's constant, they could relate the measured amount of current consumed with the number of moles involved to obtain the total number of electrons transferred per molecule of N,N-dimethylaniline. In this manner, Adams and coworkers were able to show that 2 electrons/molecule were transferred during the oxidation. With N,N-dimethyl-p-T-aniline, both para tritium atoms would be eliminated in the formation of tetramethylbenzidine. Therefore, the amount of activity remaining after the removal of all volatile products should give the amount of ortho-para coupling which took place. The results show that 20% of the N,N-dimethylaniline molecules retained their radioactivity.

The esr spectrum obtained during the oxidation of N,N-dimethylaniline at pH 2.4 had only weak, broad resonance signals giving no evidence for the presence of the dimethylanilino radical ion (XI). At high pH, the presence of one or more radical ion species is indicated. Adams and Mizoguchi[23] state that the hyperfine interaction is consistent with the tetramethylbenzidine radical ion but do not discuss their interpretation. These observations are consistent with the idea that the initial charge transfer does not produce dimethylanilino radicals, or if it does, their lifetime is too short to be detected by esr.

Galus and Adams[30] also studied the oxidation of N-methylaniline and N,N-dimethyl-p-toluidine. N-Methylaniline gave results similar to those obtained with N,N-dimethylaniline. The toluidine derivative, however, was forced to undergo a different sequence of reactions because of the blocking of the para position. They proposed a mechanism involving a two electron transfer leading to the formation of p-dimethylaminobenzaldehyde followed by a second two electron transfer leading to the formation of the benzoic acid derivative.

When Mitchell and Pausacker[31] oxidized N,N-dimethylaniline with iodosobenzene diacetate the only product isolated was tetramethylbenzidine. They suggest that the N,N-dimethylanilino radical ion, XI, is the intermediate but give no evidence for its presence. Oxidation of p-nitro-N-methylaniline with iodosobenzene diacetate produced p-nitroaniline and formaldehyde as well as the expected N,N'-dimethyl-4,4'-dinitroaniline. To account for the production of p-nitroaniline and formaldehyde, Mitchell and Pausacker propose a mechanism which is virtually identical to that proposed by Barnes and Mann for the production of aldehydes by the electrolytic oxidation of primary amines.

The question of a one or two electron charge transfer also arose when p-phenylenediamine was oxidized electrolytically[32,33] at carbon paste electrodes. Chronopotentiometry studies gave inconclusive evidence as to the number of electrons transferred during oxidation. The split wave character of the chronopotentiograms depended upon electrode material, mass transport and other experimental conditions. Cyclic voltammetry curves, on the other hand, showed an almost reversible redox system involving an equilibrium between diamine and diimine, a two electron process. No indication of a two stage anodic wave was observed. However, when the oxidation was carried out directly in the microwave cavity of an esr spectrometer Adams and coworkers observed the spectrum of the p-phenylenediamine radical ion. They suggest that a molecule of p-phenylenediimine reacted with a molecule of starting material to produce two of the radical ions.

AMIDES

O'Donnell and Mann[34,35] studied the electrolytic oxidation of aliphatic amides using cyclic voltammetry and exhaustive electrolysis. The results showed a one electron irreversible oxidation, but only one slow sweep rate, 10 v/sec., was reported and, consequently, the irreversibility of the electron transfer step is questionable. The products are protonated starting material and succinonitrile with small amounts of protonated dealkylated amide and aldehyde also produced when N-substituted amides are used. The proposed mechanism involves initial electron abstraction from the nitrogen atom, as with amines, to produce a radical ion, which can then abstract a hydrogen atom from the solvent, acetonitrile, to produce protonated amide and

acetonitrile radicals. Two acetonitrile radicals can then couple to produce succinonitrile. With water present, a competing reaction also takes place in which the amide radical ion reacts in a manner analogous to path A of the mechanism for the oxidation of primary aliphatic amines to give large amounts of aldehyde and protonated dealkylated amine. The peak potentials for the oxidation of amides are divided into three classes according to the number of N-alkyl substituents: primary amides, approximately 2.02 v; secondary amides, approximately 1.8 v; and tertiary amides, from 1.22 to 1.51 v. The oxidation of aliphatic amides requires a higher potential than for aliphatic amines because of the higher electron withdrawing power of the carbonyl group.

Addendum: Later cyclic voltammetry studies by Adams and coworkers[36] on the electrolytic oxidation of triarylamines, utilizing more rapid sweep rates than that used in the studies of N,N-dimethylaniline, indicate that the mechanism involves a reversible one electron transfer. The previous work using the slow sweep rate was complicated by the chemical reaction producing tetramethylbenzidine which occurred at such a rate as to make the oxidation appear as an irreversible two electron transfer.

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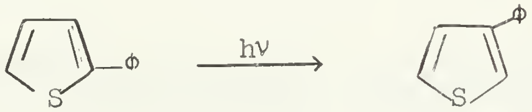
THE PHOTOCHEMISTRY OF THIOPHENES

Reported by Richard E. Peavy October 19, 1967

A great deal of work has been devoted to comparing the reactions of thiophenes to those of the corresponding benzenes and a remarkable similarity has been found to exist in both the nucleophilic and electrophilic nature of these two systems.[1,2] Recent studies, however, have indicated that the photochemical behavior of these two systems is not as similar as their more classical thermal reactions. It is the purpose of this seminar to review the recent work on the photochemistry of thiophenes and to correlate this with other benzenoid systems.

ARYLTHIOPHENE REARRANGEMENT

During the course of a study of photoarylations with iodothiophenes, Wynberg and van Driel[3] noted that the photolysis of 2-phenylthiophene in benzene solution in the presence of sodium thiosulfate formed 3-phenylthiophene (eq 1) as the only product exclusive of an intractable precipitate which deposited on the lamp. They also observed that 2,2'-dithienyl produced a mixture of 2,3'-dithienyl and 3,3'dithienyl on photolysis in benzene (eq 2). Irradiation of 2,3'-dithienyl gave 3,3'-dithienyl with no detectable amount of any other product (eq 2).



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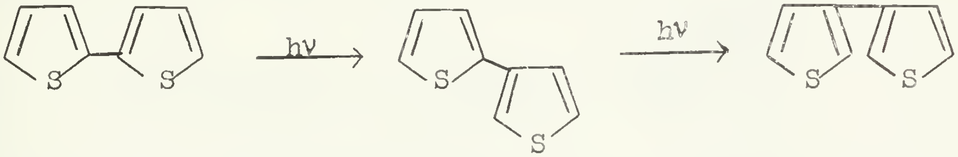
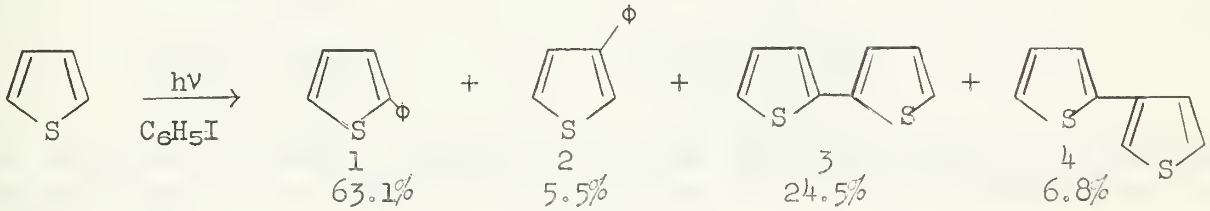


(2)

Photoarylations are a common synthetic route to substituted thiophenes[4,5] and another group independently observed a similar result.[6] They phenylated thiophene under various free radical conditions (dibenzoyl peroxide, phenylazotriphenylmethane and photolysis) and obtained mixtures of the products 1-4 with compositions dependent

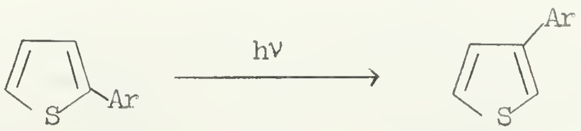


1 63.1%
2 5.5%
3 24.5%
4 6.8%

on the reaction conditions. Photolysis of thiophene in iodobenzene in the presence of metallic silver gave the above products in the indicated amounts. A control experiment established that the formation of 3 and 4 originated from the direct photolysis of thiophene. It seems likely that 2 was produced from 1 and 4 arose from 3 through rearrangement.

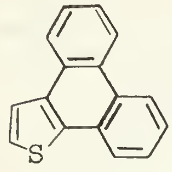
Extending his work, Wynberg noted[7] that 2-phenylthiophene formed 3-phenylthiophene without the added presence of sodium thiosulfate and that the reaction occurred in other solvents in addition to benzene. No new products were obtained in the other solvents and qualitative rate studies showed no change in the rate of decomposition of the 2-phenylthiophene in ether solution at -40° and 20°C.

The scope of the reaction was investigated and it was found that many other aryl substituted thiophenes underwent rearrangement. Photolysis of the 3-substituted



Ar = *p*-tolyl, mesityl, α- and β-naphthyl

isomers produced only decomposition. In the photolysis of the p-tolythiophene and the α- and β-naphthylthiophenes no rearrangement occurred in the aromatic ring.



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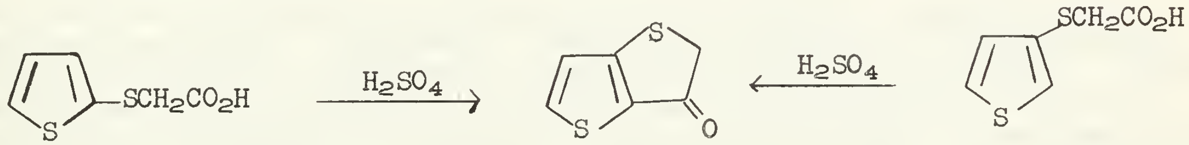
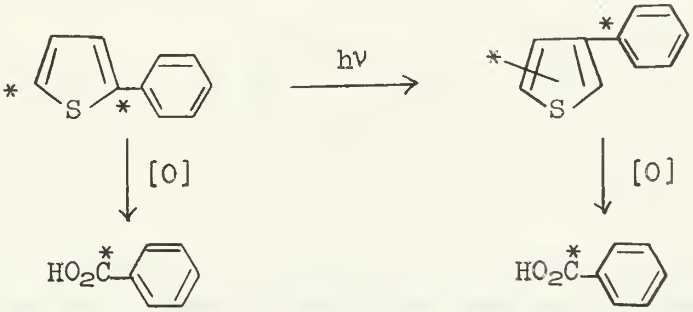
Irradiation of 2,3-diphenylthiophene gave 5 as the only product while 3,4-diphenylthiophene gave 5 as the major product and 2,4-diphenylthiophene as the minor product.

The rearrangement of 2-phenylthiophene is similar to the acid catalyzed rearrangement of thienylthioacetic acid first observed by Challenger and Holmes in 1953[8] and studied more recently by Gronowitz and co-workers.[9,10] They found that treatment of the 2- and 3-substituted isomers with concentrated sulfuric acid gave only one product resulting from migration of the thioglycolic acid group from the 2- to the 3-position.



In order to elucidate the rearrangement further, Wynberg and associates prepared and photolyzed 2,5-C^{14}-2-phenylthiophene.[11] The product of this reaction and the starting labeled material were then oxidized[12] and analyzed. The results establish

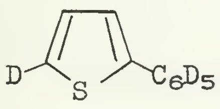


0.0310 ± 0.0003 mcuries/mole

0.0318 ± 0.0007 mcuries/mole

that the phenyl group remains attached to the same carbon atom during the rearrangement and consequently there must be an interchange of the 2- and 3-carbon atoms in the thiophene ring.

The desirability of tagging the remaining carbon atoms in the thiophene ring now presents itself. In order to accomplish this, Wynberg and Kellogg resorted to deuterium labeling.[13,14] Because of the overlap of the nmr chemical shifts of the thienyl and benzene ring protons, it was necessary to use pentadeuteriophenyl isomers. The investigators therefore prepared[14] the deuteriothiophenes 6 and 7.



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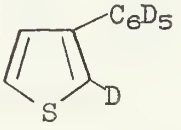

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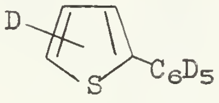

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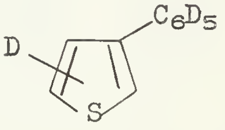

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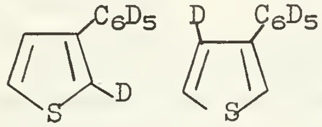
Irradiation of 6 in ether solution was carried out for six hours after which time approximately equal amounts of 2- and 3-substituted isomers were present. These were separated by gas chromatography to give two products, 8 and 9.

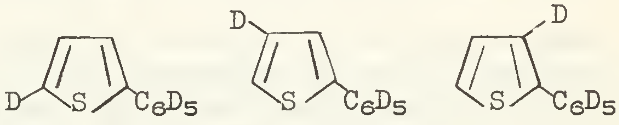
The two mixtures were analyzed by nmr. Gronowitz et. al.[2,15] have done detailed nmr studies of deuterated and substituted thiophenes and from these studies have been

able to assign chemical shifts and coupling constants to specific protons in the thiophene ring. Using this information and the information obtained from the comparison of the nmr spectra of the products with the nmr spectra of the starting materials, the authors were able to estimate the amounts of the various positional isomers present. Thus, comparison of the nmr of 3-pentadeuteriophenylthiophene with that of 7 and 9 allowed the investigators to estimate the composition of mixture 9 to be as shown. Analogously, comparison of the nmr of 2-pentadeuteriophenylthiophene with 6 and 8 led to the composition of mixture 8 as shown. Photolysis of 7 was carried out as a control and although the recovered product was pure 7 relative to glpc, examination of its nmr spectrum indicated that it contained equal amounts of isomers 10 and 11.



7 5-10%   10 0-5%   11 85-90%

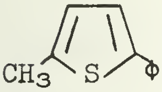
Mixture 9



6 75-80%   12 10%   13 10%

Mixture 8

It is evident from these results that the rearrangement occurs with a high degree of specificity and that a small amount of further rearrangement is also occurring. It is doubtful that deuterium migration is involved since the more migration-prone phenyl group remains attached to the same carbon atom.



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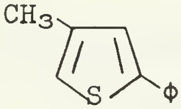

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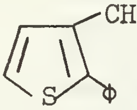

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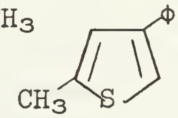

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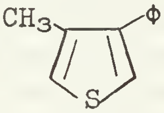

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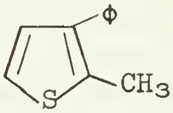

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Synthetic difficulties prevented the labeling of the remaining carbon atoms with deuterium so the authors prepared the various phenylmethylthiophenes[16] in order to identify all the carbon atoms after the rearrangement. The compounds 14 through 19 were photolyzed in ether solutions with a high-pressure mercury lamp for six hours. Products were identified by their gas chromatography retention times on two different columns. The results are summarized in Table I.

Table I

Starting Material	Percent Product					
	14	15	16	17	18	19
14	80.0	0.8	0.3	17.1	1.1	0.7
15	0.5	53.1	1.5	2.9	37.7	4.3
16	0.1	0.03	75.6	0.1	2.6	21.6
17	0.1	0.6	0.4	95.5	3.0	0.4
18	0.8	0.1	12.1	0.8	69.9	16.3
19	1.1	0.3	< 4.2[a]	4.9	19.1	70.4

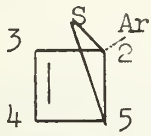
a) absolute maximum value

Examination of the photolyses of 16, 18 and 19 as a function of time showed that the product ratios remained relatively constant, indicating that the products were the result of the primary photochemical process.

The table shows that the 2-phenyl derivatives are still undergoing a very specific rearrangement. The products obtained in the photolysis of 2-phenyl-5-methylthiophene are roughly in the same amounts as those obtained from 2-pentadeuteriophenyl-5-deuteriothiophene, indicating that substitution of a methyl group

for a deuterium atom has not altered the mechanism of the rearrangement. The predominate rearrangement in the 2-phenyl isomers still involves the inversion of carbon atoms 2 and 3 with a small amount of scrambling of the other carbon atoms. The predominate reaction in the 3-phenyl isomers, however, appears to be an interchange of the C_2 and C_4 atoms and the C_2 and C_5 atoms with additional scrambling also occurring.

The authors had originally proposed[3,11] that the mechanism of the rearrangement of 2-arylthiophenes might involve the valence bond isomers 20, 21 and 22 analogous to the benzene valence bond isomers Dewar benzene 23, Ladenburg (prismane) benzene 24 or benzvalene 25. That the three valence bond isomers of benzene do indeed exist is now well established[17] and the subject has been reviewed recently.[18] Such isomers have been postulated as intermediates in numerous photolytic reactions[19] and two reviews of valence bond isomerizations have recently been published.[20]



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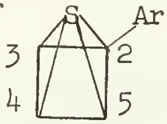

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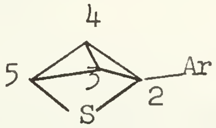

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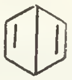
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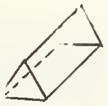
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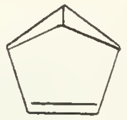
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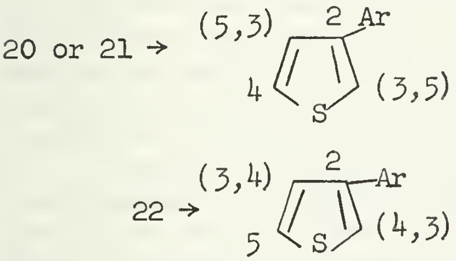
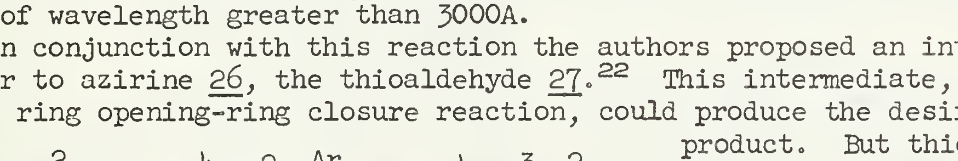
Examination of the valence bond isomers 20, 21 and 22, however, shows that they do not predict the correct labeling results obtained earlier.[21,22] Thus, Dewar structure 20 and prismane 21 predict only a relative change in the position of the sulfur atom. Rearrangement through isomer 22 would effect equivalence of C_3 and C_4. This would create an equilibrium between two possible isomers allowing the formation of two products in equal or near equal amounts and this is not observed experimentally (even allowing for a sizable substituent effect both isomers should be formed to some extent).



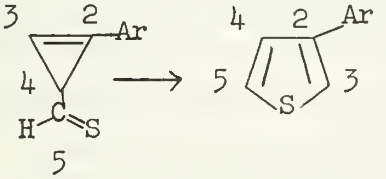
Heterocyclic analogs of benzenoid valence bond isomers are at present unknown although several photorearrangements of related interest are known.[23] One such rearrangement is the formation of 2,5-diphenyloxazole from 3,5-diphenylisoxazole.[24] The azirine 26 has been conclusively identified through isolation and characterization as the intermediate involved in the reaction. In addition,



26

the irradiation of 26 gives product directly, and more rapidly than does irradiation of the isoxazole. Azirine 26 reverts back to starting material when irradiated with light of wavelength greater than 3000A.

In conjunction with this reaction the authors proposed an intermediate formally similar to azirine 26, the thioaldehyde 27.[22] This intermediate, obtained by a formal ring opening-ring closure reaction, could produce the desired rearranged product. But thioaldehydes are generally considered to be very unstable[25] and other reactions could also result from 27. For this reason the specificity seen in the rearrangement would not be predicted by 27. Another alternative, thioketone 28, may be ruled



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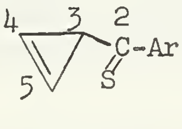
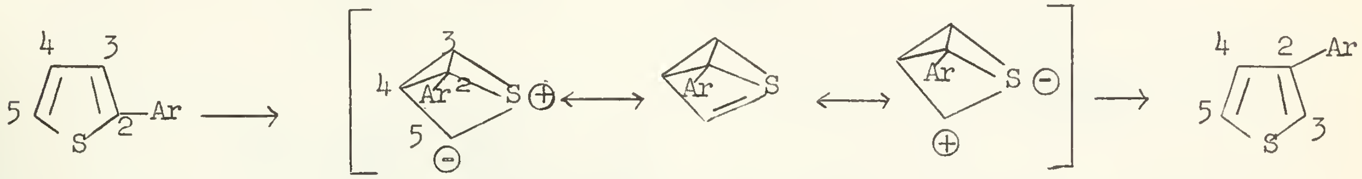


28

out as a possible intermediate because it would equilibrate carbon atoms 4 and 5 instead of giving phenyl migration.

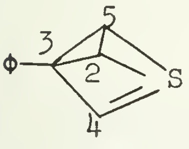
A further mechanistic proposal offered by Wynberg and co-workers[21,22] requires the interaction of the sulfur d-orbitals with the π-electrons of the C_2-C_3 bond to form species 29. This species could rearrange to the desired product as illustrated.



29

At this point the question arises concerning the d-orbital resonance of the sulfur atom with the π-electrons of the double bond system in thiophene. There is little doubt that sulfur is capable of and indeed does undergo d-π bonding. Doering and Hoffmann[26] studied the deuteroxide-catalyzed hydrogen-deuterium exchange of the α-proton of tetramethylammonium, tetramethylphosphonium and trimethylsulfonium ions with deuterium oxide. They observed an acceleration in rate proceeding from the ammonium to the phosphonium to the sulfonium ion and they attributed this to the d-orbital stabilization of the transition state for carbanion formation. Many other examples are also known.[27] However, the extent of interaction of the sulfur d-orbitals in thiophene with the π-electrons of the double bonds is a point of controversy. Longuet-Higgins[28] used a simple LCAO method taking the sulfur d_{yz} and and d_{xz} orbitals into account and noted a similarity between the predicted reactivities of thiophene and benzene while Shomaker and Pauling[29] used valence bond theory to demonstrate the same result. However, calculations performed by other workers[30] neglecting the d-orbitals of sulfur have arrived at results which predict reactivities similar to those observed experimentally. Thus, no definite conclusion has been reached on the importance of d-orbital effects in thiophene.

Present evidence cannot rule out the existence of 29 as an intermediate in the rearrangement of 2-arylthiophenes. There is no precedent for such a species taking part in an excited state reaction although there are stable ylids which participate in ground state reactions.[31] The reaction has been observed to proceed at a faster rate in more polar solvents which would lend credence to its presence but it is not clear if this rate enhancement is due to some solvent effect on the excited state or is actually a measure of the photorearrangement. The authors have not detected any intermediates by conventional means so if there are any present, they must be relatively short-lived. And virtually no information is available on the nature of the excited states involved but the fact that there is no oxygen effect seems to favor reaction through an excited singlet or vibrationally excited ground state.



30

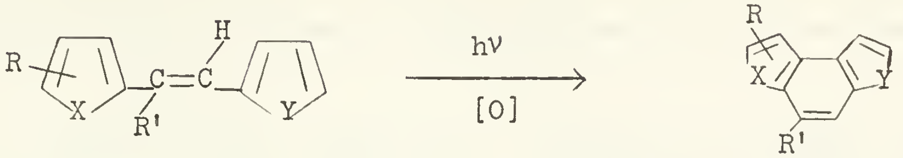
An intermediate capable of explaining the major products in the rearrangement of 3-arylthiophenes is 30 although its formation is difficult to rationalize.[22] It would account for the major products resulting from interchange of C_2 and C_4 and of C_2 and C_5. Although both species 29 and 30 are novel, they are the most promising intermediates postulated thus far as they account for the major portion of the products formed.

It is interesting to note that diphenylfurans[32] do not undergo phenyl migrations upon irradiation which suggests that sulfur may play a role that oxygen cannot perform. The possibility that other elements of the third row in the Periodic Table (containing empty d-orbitals) may function in a similar manner in excited state reactions is an interesting premise.

STILBENE-LIKE PHOTOCYCLIZATIONS

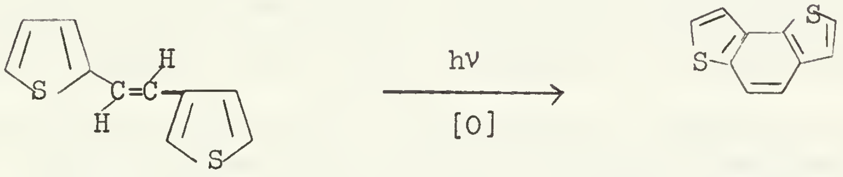
Extending the study of the photochemistry of thiophenes further, Wynberg and co-workers found that irradiation of 1,2-dithienylethylenes produced phenanthrothiophene derivatives.[33] The reaction was found to occur only in the presence of

an oxidizing agent such as iodine or oxygen. The results are summarized below.



33 (a-f)

31a, X=Y=S, R=R'=H
b, X=Y=S, R=4-CH_3, R'=H
c, X=Y=S, R=5-CH_3, R'=H
d, X=Y=S, R=H, R'=CH_3
e, X=S, Y=O, R=R'=H
f, X=Y=O, R=R'=H



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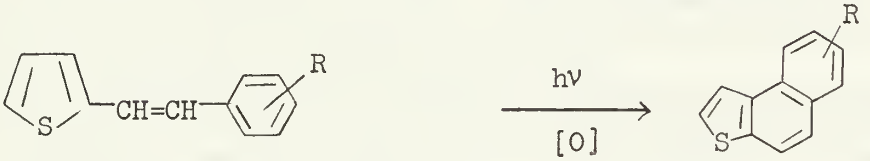
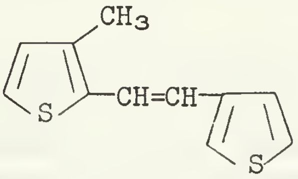
34

Carruther and Stewart had observed the same reaction with thienylstilbenes.[34]



(3)

Wynberg and co-workers[33] also found that irradiation of 35 in the presence of iodine produced 33a resulting from the expulsion of the methyl group and that 3,3'-dithienylethylene, 36, did not form any product on photolysis. Carruther and Stewart had



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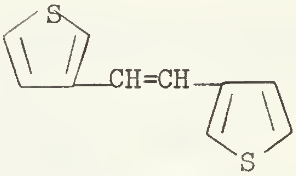


36

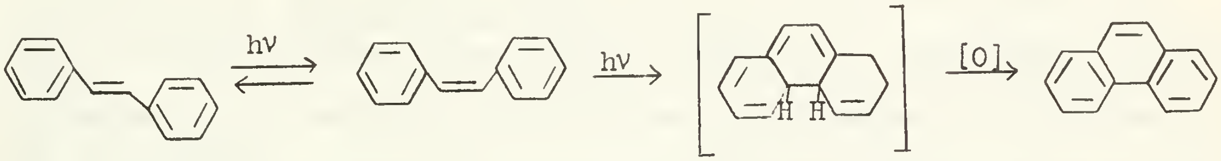
also noted the expulsion of a methyl group in their study. Thus, when R = o-CH_3 in eq. 3, the products obtained were the 7-methyl derivative and the unsubstituted product.

These photo-oxidative ring closures are analogous to the photocyclizations of stilbenes with the subsequent formation of phenanthrenes. This type of reaction has been reviewed recently[35] and since it has important bearing on the mechanism involved in the cyclizations of thienylethylenes, a brief summary of the reaction will be presented here.

Stilbene cyclizations are a special case of the more general reversible cyclization of 1,3,5-hexatriene to 1,3-cyclohexadiene. Srinivasan has studied this latter reaction extensively[36] and the subject has been reviewed.[37]

The mechanism of the stilbene ring closure has been a controversial topic for several years but present evidence favors one mechanism over other alternatives.

This mechanism[35,38] involves an initial photoisomerization of trans-stilbene to cis-stilbene with the attainment of a steady state. The cis-stilbene, on further photochemical excitation to the first excited singlet state, ring closes to form dihydrophenanthrene which, on oxidation, yields phenanthrene as the final product.



Evidence for the existence of a dihydrophenanthrene intermediate includes spectroscopic observation[35,38,39] as well as isolation of two stable 9,10-dihydrophenanthrenes.[40] The stereochemistry of the intermediate is still open to question but it is believed to be trans in the liquid phase cyclization.[35]

Examination of the photolysis of dithienylethylenes by means of gas chromatography enabled Wynberg and his associates to detect an initial cis $\leftrightarrows$ trans equilibrium. When the trans isomer was irradiated in the presence of iodine, a new peak, corresponding to the cis isomer, was observed in the glpc trace. If the irradiation was stopped at this point, the cis isomer slowly reverted to the trans-ethylene.

When the irradiations were carried out in degassed cyclohexane solutions with light of 350 mu, yellow solutions were produced which gave clear absorptions in the ultraviolet. Thus, 36 (which fails to give a phenanthrothiophene) produced a yellow solution on irradiation which exhibited an absorption at 420 mu. Exposure of this solution to visible light caused a rapid disappearance of the yellow color and of the ultraviolet absorption as well. Other dithienylethylenes produced similar solutions and exhibited absorptions between 415 and 360 mu. These solutions remained yellow for 12-15 hours if kept in the dark.

This yellow coloration is also produced in stilbene cyclizations and is attributed to the dihydrophenanthrene intermediate. It is therefore likely that the yellow color produced in the photolysis of dithienylethylenes is caused by the corresponding dihydrophenanthrothiophenes.

The above evidence supports the hypothesis that the photo-oxidative ring closure of dithienylethylenes proceeds in a manner analogous to stilbene ring closures. Further experimentation is necessary, however, before the mechanism becomes entirely clear.

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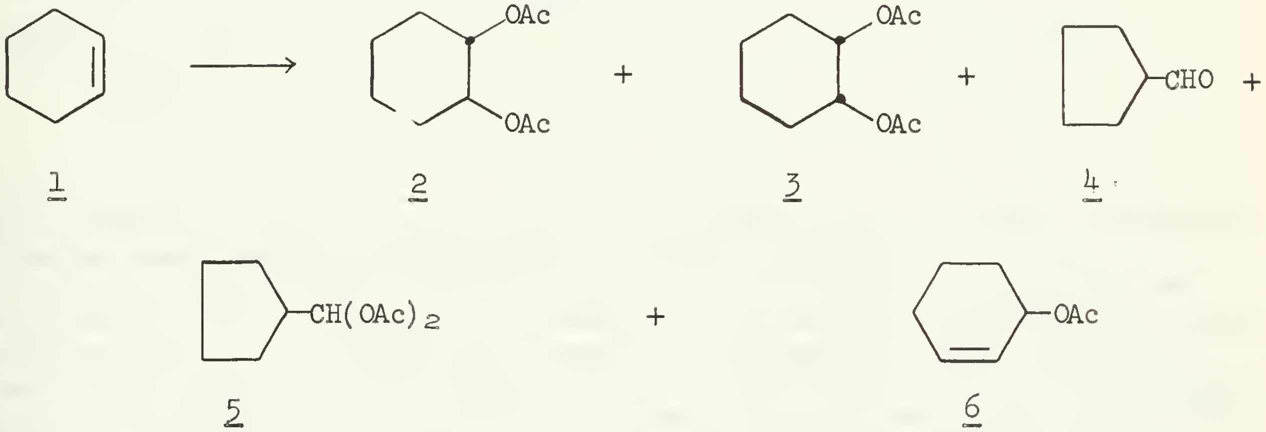
ALLYLIC OXIDATION OF OLEFINS WITH METAL ACETATES

Reported by Joel L. Kirkpatrick October 23, 1967

INTRODUCTION

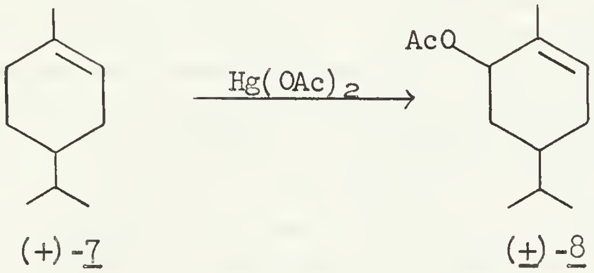
The treatment of olefins with lead^{IV} acetate,[1] thallium^{III} acetate,[2,3] mercury^{II} acetate and palladium^{II} acetate[4] often gives a confusing variety of products depending upon the solvent and reaction conditions. Most of these products are presumed to arise from an initial oxymetallation adduct. The reaction of $Hg(OAc)_2$ with olefins to give stable oxymercuration products is well known.[5,6] On the other hand, stable oxyplumbation and oxypalladation compounds have not been isolated and only recently have oxythallation adducts from styrene and o-allylphenol been reported.[7]

Allylic oxidation of olefins is common to all the metal acetates cited above. When cyclohexene (1) is treated with the different oxidizing agents[2,3,8] 3-acetoxycyclohexene (6) is produced in about 10% yield with $Tl(OAc)_3$,[2,3] in 37% yield with $Pb(OAc)_4$[3] and as the only product with $Pd(OAc)_2$[3] and $Hg(OAc)_2$.[2,3] With $Pb(OAc)_4$ and $Tl(OAc)_3$ the other products isolated were cis- and trans-1,2-diacetoxycyclohexane (2, 3), C-formylcyclopentane (4) and its diacetate (5). These products are consistent with initial oxymetallation followed by reactions involving carbonium ions.



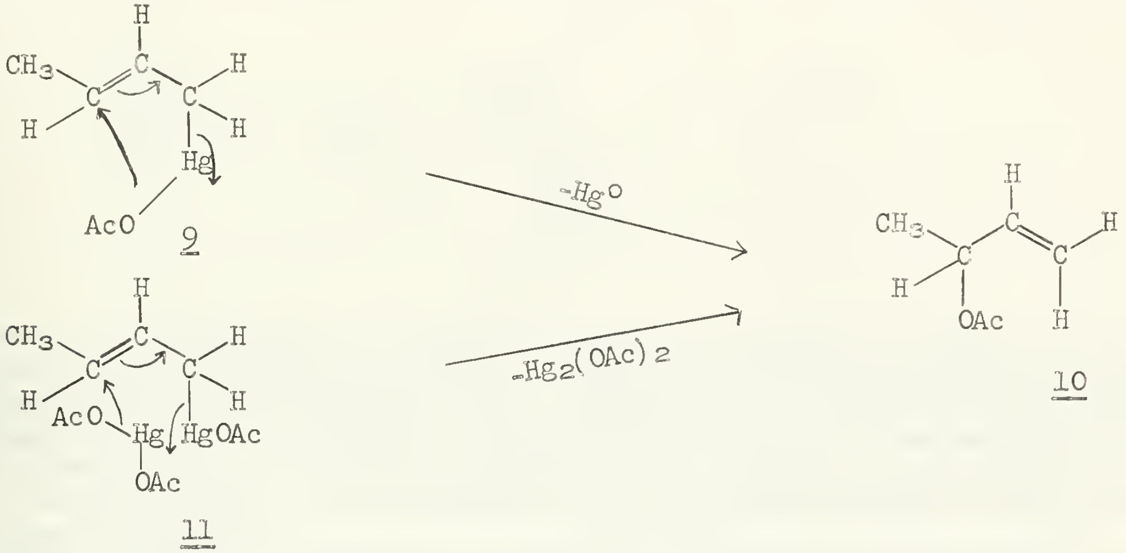
REACTION WITH $Hg(OAc)_2$

When (+)-carvomenthene (7) was treated with $Hg(OAc)_2$, the product isolated was (±)-carvotanacetol acetate (8)[9,10] which gave (±)-carvotanacetone on hydrolysis and oxidation. Wiberg and Nielsen[8] showed both starting material and product were configurationally stable under the reaction conditions. From this it was concluded a symmetrical intermediate, presumably the allyl radical or cation, was involved. When cyclohexene-C^{13}, having 0.332 ± 0.004% excess C^{13} in the olefinic carbons was reacted with $Hg(OAc)_2$, 3-acetoxycyclohexene was isolated.[8] Hydrogenation, hydrolysis and oxidation gave cyclohexanone which was degraded by the method of



Loftfield[11] to give the carbonyl carbon as carbon dioxide. Analysis of this indicated that the carbon attached to the acetoxy group had 0.158 ± 0.018% C^{13} which is very close to the 0.166% expected for a symmetrical cation (or radical) as an intermediate.

Sleezer, Winstein and Young[12] found that butenyl-HgOAc (9) undergoes a demercuration reaction of an S_Ni' type to give Hg^0 and pure allylic acetate (10), at least 99.5% secondary, with a rate of ca. 8×10^{-7} sec.$^{-1}$ at 25°C. In the presence of 0.0565 M added $Hg(OAc)_2$, the rate was greatly increased, k being 2.2×10^{-4} sec.$^{-1}$ at 25°. While the inorganic product was now $Hg_2(OAc)_2$, the organic product remained the allylic acetate (10). A mechanism such as the one symbolized in 11 can be used to explain this $Hg(OAc)_2$ promoted reaction.



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11

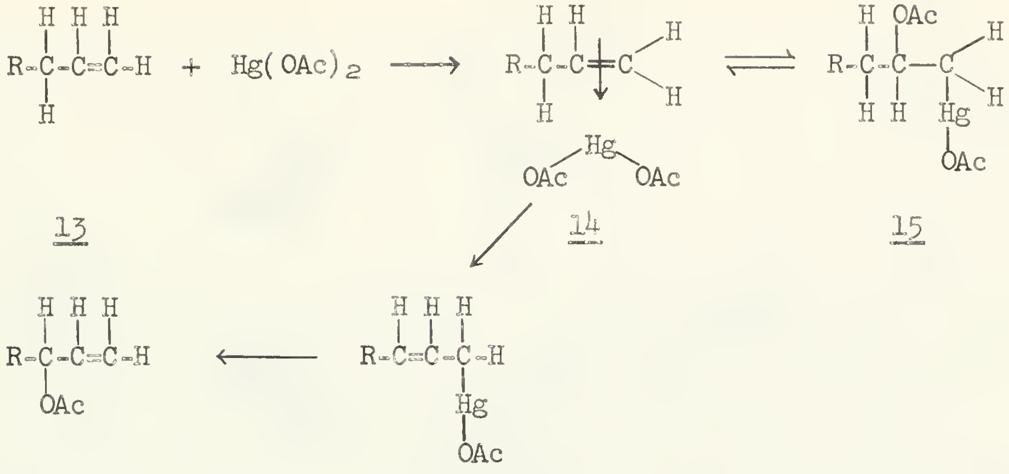
10

It had been found[13] that pure allyl-HgX derivatives exhibit nmr spectra for ordinary σ-allyl structures, but, when catalysts such as HgX_2 salts were added, nmr spectra with an AX_4 proton pattern for rapidly equilibrating σ-allyl species were observed. In contrast, in the butenyl-HgX system, even under conditions for rapid allylic equilibration, the nmr spectra are those for the primary butenyl structure. These results parallel those found in the analogous Grignard compound,[15] where equilibrium lies far to the primary side. Therefore if allylic oxidation of 1- and 2-butene by $Hg(OAc)_2$ proceeds via allylic mercurials, and transition state energies reflect the ground state energies of these, secondary acetate (10) would be expected from either. Any secondary mercurial initially formed from 2-butene should rapidly become primary under the reaction conditions and give the secondary acetate.

Winstein and co-workers[14] treated several 1- and 2-olefins with $Hg(OAc)_2$ and found the initial composition of the allylic acetate mixture in the presence of excess olefin to be nearly pure secondary ester, although at equilibrium the primary ester predominates. The inorganic product is Hg^0 when the olefin is in excess and $Hg_2(OAc)_2$ in the presence of excess $Hg(OAc)_2$. Conclusions drawn from the isolation of $Hg_2(OAc)_2$ should be questioned since Hg^0 is known to be oxidized by Hg^{II} to give Hg_2^{I}. Small amounts of other monoacetates, possibly enol acetates, were observed but diacetates were not found. The percentage of secondary isomer drifts down as the reaction progresses which is probably due to $Hg(OAc)_2$ catalyzed isomerization of the allylic esters. This was demonstrated independently by treating crotyl acetate and α-methylallyl acetate with $Hg(OAc)_2$. It was found for the latter that after 23 hrs. at 75° in acetic acid with 0.242 M α-methylallyl acetate and 0.296 M $Hg(OAc)_2$, 38% of allylic esters were recovered, 40% secondary- 60% primary.

A normal carbonium ion or radical mechanism was felt to be inconsistent with the observation that secondary allylic acetate from both 1- and 2-olefins was the exclusive product. It was felt that only by allylic mercurials which rapidly equilibrated to the primary allylic mercuric acetate, which would then undergo demercuration to secondary acetate could this be explained.

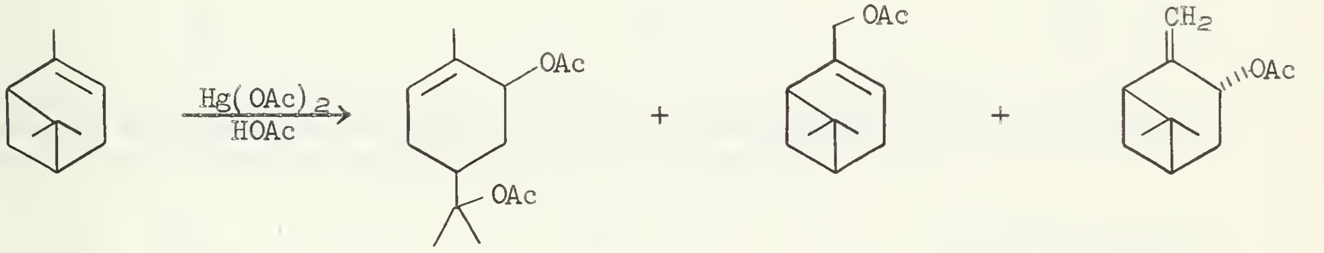
The mechanism of the reaction can be formulated as below. The reaction of the



13 14 15 17 16

1-olefin (13) with $Hg(OAc)_2$ is presumed to give an initial π-complex (14) (a yellow color has been observed upon mixing the olefin and the $Hg(OAc)_2$) which is in equilibrium with the oxymercurial (15). Elimination from 14 either by a S_E2' or S_Ei' pathway to give the primary mercurial (16) followed by rearrangement by an S_Ni' mechanism (9) or by $Hg(OAc)_2$ promotion (11) would give the secondary acetate (17). For the 2-olefin, an equilibration to the primary mercurial would then give the observed product.

That carbonium ion pathways are operating is evident by the products, sobrerol diacetate (19), myrtenyl acetate (20) and pinocarvyl acetate (21), isolated from α-pinene (18) and $Hg(OAc)_2$ in acetic acid.[10] Only 21 would be expected if the



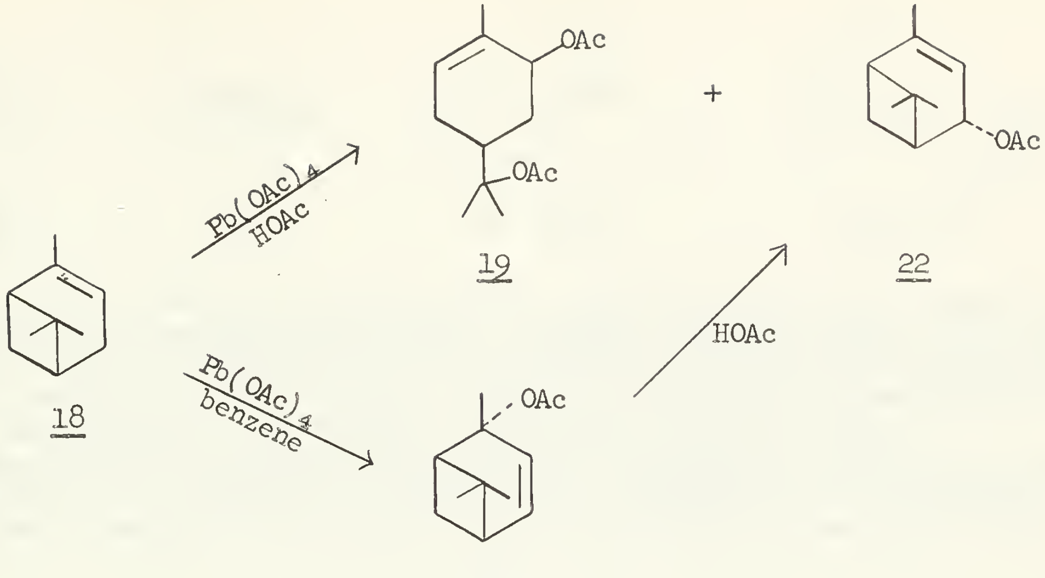
18 19 20 21

mechanism involving a rapidly equilibrating pair of σ-alkyl mercurials were operating and the transition state resembled the starting mercurial. The validity of comparing a bicyclic olefin and an open chain olefin is questionable at best since ring strain and steric effects are absent in the latter. That the same mechanism does not operate in all cases is evident from the results of oxidation of allylbenzene with $Hg(OAc)_2$ which gave the same allylic products as obtained by demercuration of cinnamyl-HgOAc, a mixture of secondary and primary acetates.[14]

REACTION WITH $Pb(OAc)_4$

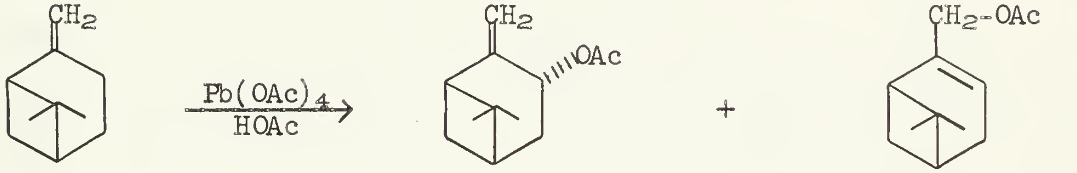
Wiberg and Nielsen[8] studied the oxidation of C^{13} labeled cyclohexene with $Pb(OAc)_4$ and found scrambling, indicative of a symmetrical cation intermediate.

The reaction of $Pb(OAc)_4$ with α- and β-pinene seem to follow two distinct reaction sequences. In acetic acid Criegee[16] reported (+)-sobrerol diacetate (19) and verbenyl acetate (22) as the oxidation products of α-pinene. Whitham[17] showed that in benzene the product was cis-2-acetoxypin-3-ene (23) which was converted to 22 upon heating in acetic acid.

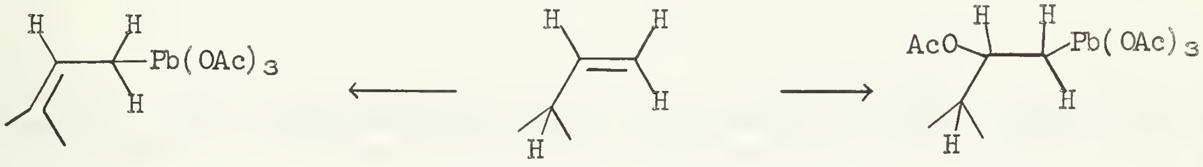


18 19 22 23

β-Pinene (24), on the other hand, gave a mixture of myrtenyl acetate (20) and pinocarvyl acetate (21).[18] The reaction of β-pinene can best be explained by assuming an organolead derivative of type 25 and α-pinene giving the products coming from an acetoxy organolead adduct of type 26.

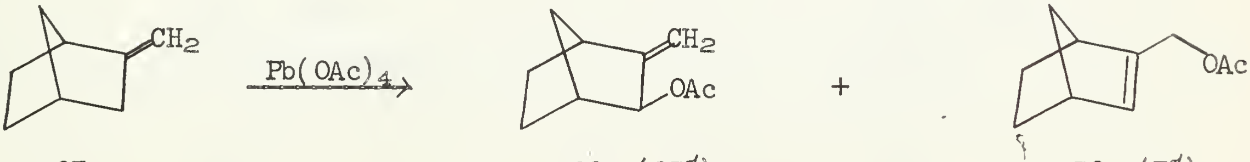


24 21 (46%) 20 (10%)

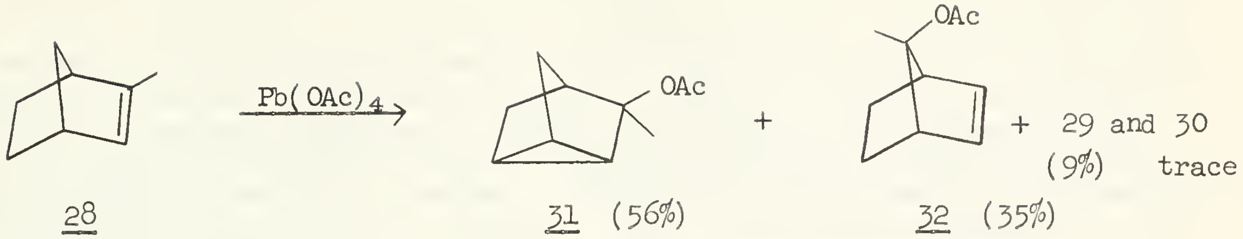


25 26

Recently Erman[19] compared the Pb(OAc)$_4$ oxidation of norcamphene (27) and 2-methylnorbornene (28) in order to attempt to discover why such a relatively small difference in structure should result in different reaction sequences. Norcamphene gave 3-exo-acetoxynorcamphene (29) and 2-acetoxymethylnorbornene (30) in 26% yield in a ratio of 93:7. Oxidation of methylnorbornene (28) under the same conditions

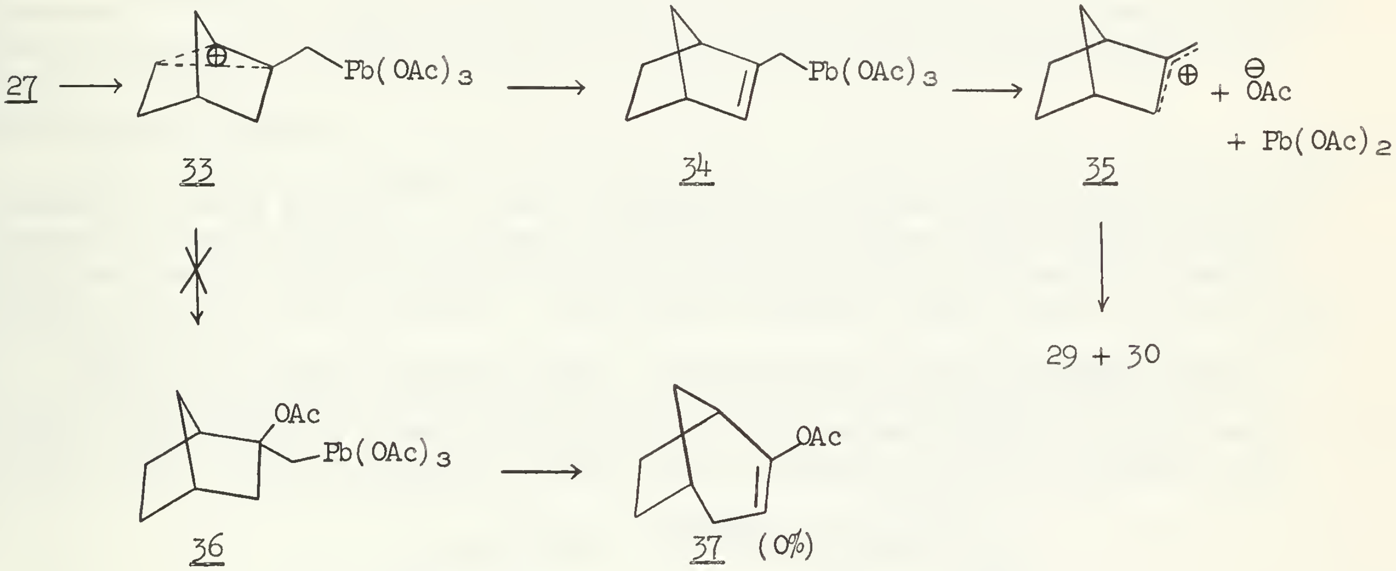


27 29 (93%) 30 (7%)

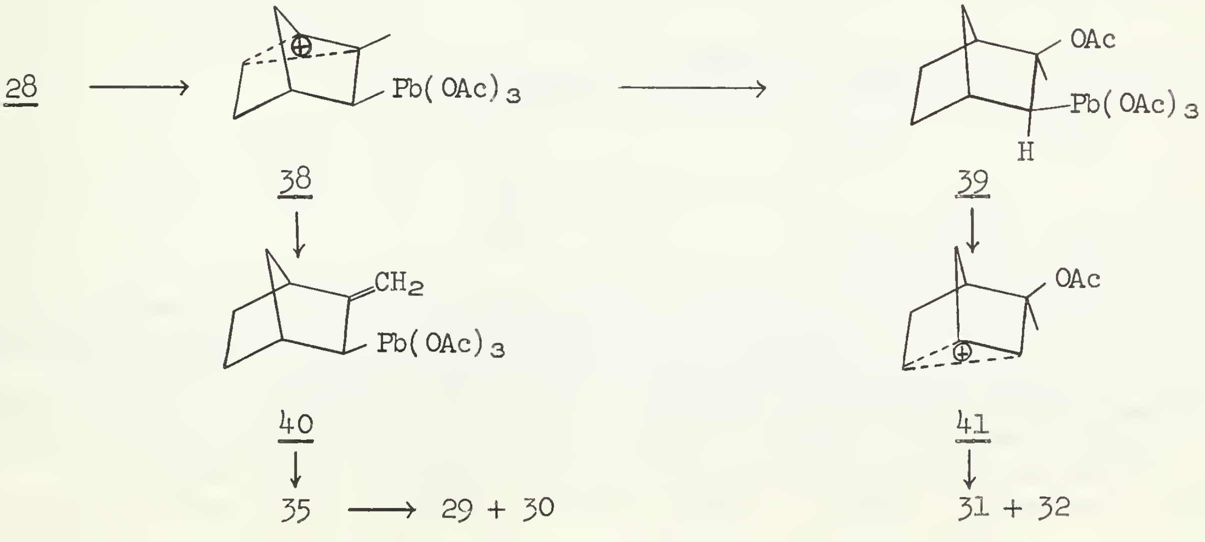


gave a mixture of 4 acetates in 35% yield: 3-methyl-3-nortricyclyl acetate (31, 56%), 7-syn-acetoxy-7-methylnorborn-2-ene (32, 35%), acetate 29 (9%) and a trace of acetate 30. Compounds 31 and 32 were identified by comparison with independently synthesized samples, 29 was hydrolyzed then oxidized to 3-ketonorcamphene and acetate 30 was identified by infrared, mass and nmr spectral study.

The results for norcamphene (27) can best be explained by assuming an initial organolead adduct 34, which should undergo rapid elimination to the mesomeric ion 35. Addition of acetate under kinetic control at the more electron deficient position



of mesomeric ion 35 would account for the product distribution. In contrast, the main products from 2-methylnorbornene must come from the acetoxy compound 39, which should eliminate to 41 faster than acetate elimination and consequently would give



31 and 32. These results parallel the products from the oxidation of norbornene.[20]

In this mechanism it is assumed that acetate should add to 33 to give acetate 36 or to 38 to give 39 by a kinetically controlled process competitive with the elimination to 34 and 40 respectively. Once formed, the allyllead derivatives 34 and 40 should undergo rapid elimination to 35. Compound 36 would be expected to eliminate to a primary carbonium ion which would give the ring enlarged enol acetate (37) by rearrangement. None was found although its stability to the reaction conditions was not determined. It must be assumed then that elimination to the trisubstituted olefin 34 occurs at a faster rate than elimination to the disubstituted olefin 40.

It can be argued that the products 29 and 30 are derived from a rapidly equilibrating pair of σ-allyllead adducts 34 and 40, which are produced directly by an S_Ei' or S_E2' mechanism.[14] By a rapid equilibration to the primary organolead isomer, followed by S_Ni' deplumbation, the secondary acetate (29) would be expected to be formed. While this possibility cannot be ruled out, Wiberg and Nielsen[8] found only the endo olefin, 6-acetoxy-1-methylcyclohexene, from the oxidation of 1-methylcyclohexene, which seems more consistent with the formation of a carbonium ion.

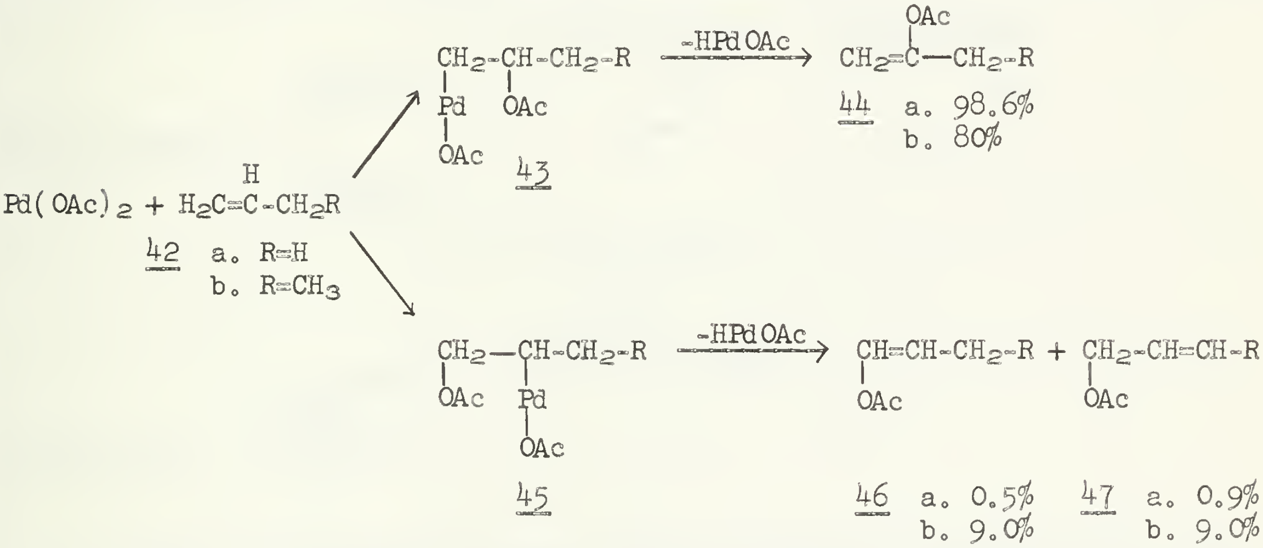
REACTION WITH $Tl(OAc)_3$

The reaction of $Tl(OAc)_3$ with olefins has been studied by several groups of workers.[2,3,7,23,24] The results discussed above with cyclohexene indicate carbonium ion intermediates. Since thallium^{III} is isoelectronic with lead and mercury, no great differences in reactivity would be expected and none has been found.

REACTION WITH $Pd(OAc)_2$

The oxidation of olefins by Pd^{II} salts under aqueous conditions to give carbonyl compounds is well known.[25-27] When cyclohexene was treated with $Pd(OAc)_2$, only 3-acetoxycyclohexene (6) was isolated.[3] In contrast with the other metal acetates discussed above, $Pd(OAc)_2$ gives mainly enol acetates with 1-olefins while mainly allylic acetates with 2-olefins.[4] The allylic acetates formed form 1- and 2-olefins are different.

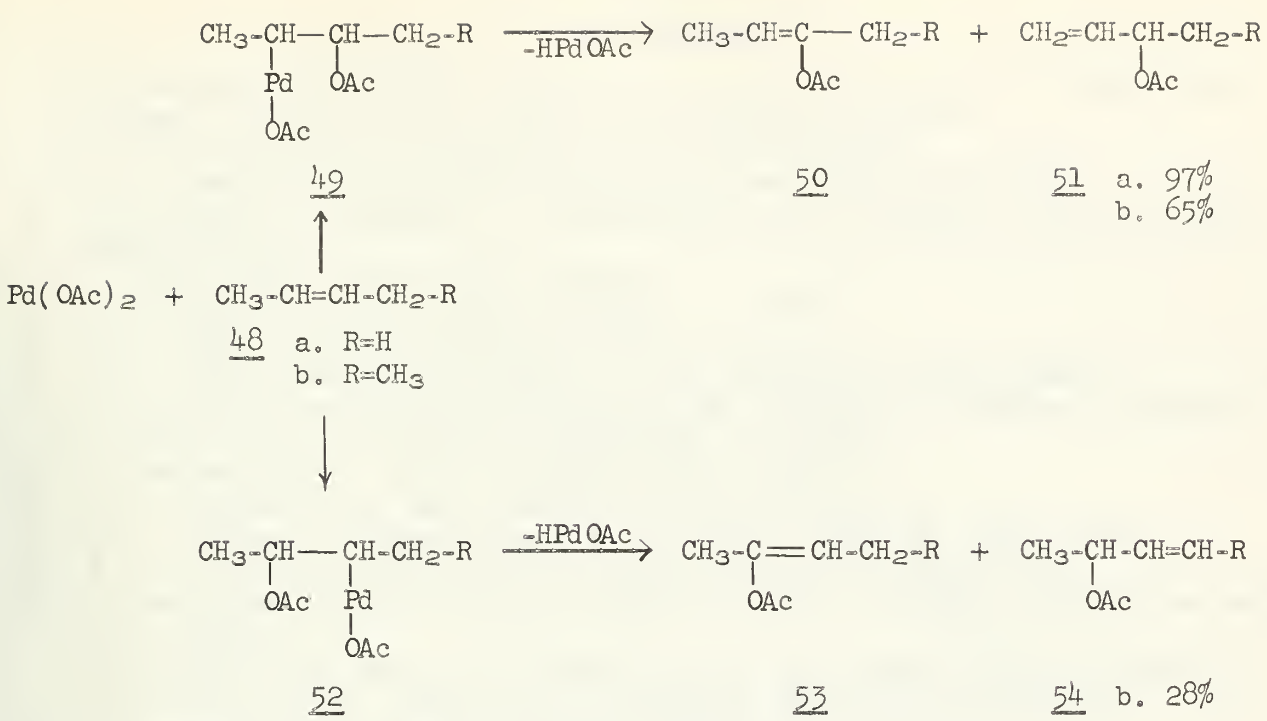
Oxidation of excess propene (42a), 1-butene (42b), cis- and trans-2-butene (48a) and cis-2-pentene (48b) by $Pd(OAc)_2$ in acetic acid proceeds smoothly at 25° to give high yields of monoacetate products. From propene, 98.6% is isopropenyl acetate (44a), 0.5% of propenyl acetate (46a) and about 0.9% allyl acetate (47a).



From 1-butene, more allylic acetate (47b) is formed, ca. 9%, and is pure primary. The major product is still the enol acetate (44b, 80%).

Both cis- and trans-2-butene (48a) give nearly exclusively the allylic acetate which is the pure secondary isomer 51a. Likewise cis-2-pentene (48b) gave 92% allylic acetates (70% isomer 51b, 30% isomer 54b) which were pure secondary.

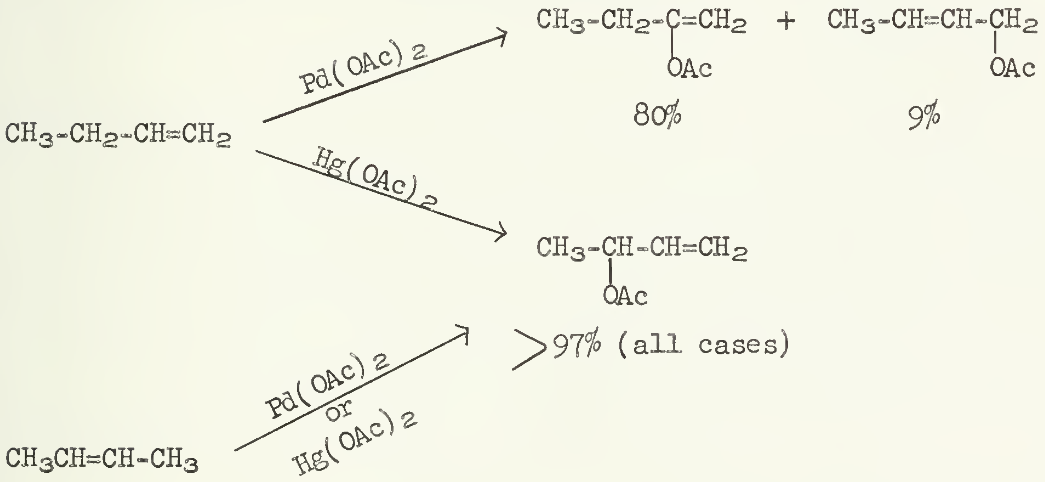
All the product distributions were taken after short reaction times in order to obtain values close to kinetic control results. $Pd(OAc)_2$ isomerized allylic



acetates, with concurrent material loss due to other reactions.

Since the $Pd(OAc)_2$ oxidation of 1- and 2-olefins gives a separate allylic acetate from each olefin, the rapidly equilibrating σ-allylpalladium species analogous to that postulated for $Hg(OAc)_2$ oxidation is ruled out. Oxypalladation of the olefins, presumably reversible, gives adducts 43, 45, 49 and 52. These eliminate elements of HPdOAc to yield either the enol acetate or allylic acetate, depending upon the direction of elimination. From the available data it can be concluded that Markovnikov addition is preferred over non-Markovnikov addition and that elimination to give allylic acetate is preferred over elimination to give enol acetate.

This can be illustrated with 1- and 2-butene as shown below:



A possible explanation of this difference may be in the stability of the oxymetallation intermediate formed initially. The oxymercurial is relatively stable and elimination of HOAc is faster than elimination of the elements of HHgOAc. When the oxypalladation compound forms, it may immediately lose HPdOAc to give the observed products.

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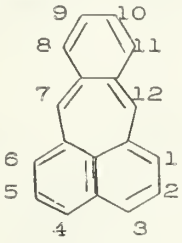
THE PLEIADENE RING SYSTEM

Reported by Spencer M. Krueger October 26, 1967

INTRODUCTION

In 1933 Fieser[1] suggested the trivial name "pleiadene" for the "truly aromatic, anthracene-like hydrocarbon" 1. However, later the term was used by several groups of workers[2,3] to refer to the simpler compound 2 and "benzopleiadene" to hydrocarbon 1. In this seminar the terms "pleiadene" and "cyclohepta[de]naphthalene" will be used in reference to 1 and 2, respectively, in accord with the more recent work of Lansbury[4] and Cava.[5]

Since a summary of the synthesis and properties of 2 can be found in a review of non-benzenoid aromatics,[6] only the recent chemistry of the potentially aromatic pleiadenes and their dihydro analogues (3) will be discussed in this seminar.



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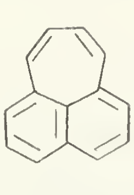

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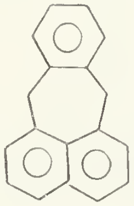
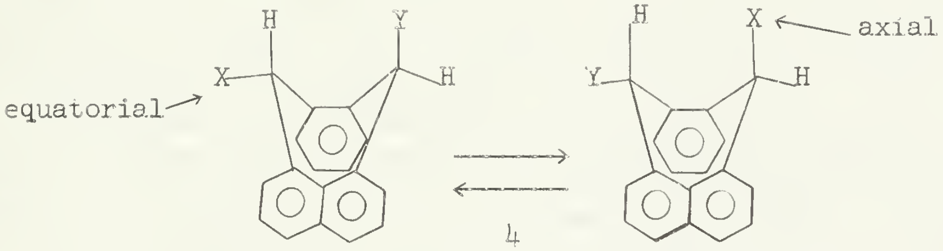


3

DIHYDROPLEIADENES

Unlike pleiadene itself, 7,12-dihydropleiadenes (DHP) are not planar molecules but exist in two possible conformations (4). When X=Y one conformer inverts into itself. However, when $X \neq Y$ the two conformers are diastereoisomers. This possibility of two conformations, in which the substituents are axial in one and equatorial in the other, had led to some interesting inversion, conformational, and transannular reaction studies.



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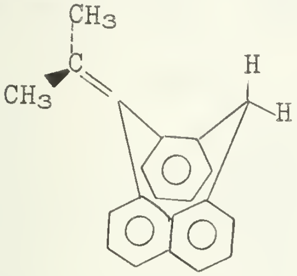
Lansbury and co-workers have investigated the rates of inversion of several DHP's by variable temperature nmr.[7] For some DHP's (4, X=H) in which at least one methylene group is present, the inversion rate at the coalescence temperature can be calculated from Gutowsky's expression[8] $k=\pi\delta_{AB}/\sqrt{2}$, in which δ_{AB} refers to the chemical shift difference between the equatorial and axial protons. Identical ΔF^* ($\pm$0.2 kcal/mole) values were obtained when the rates of inversion were calculated using the AB quartets of both the C_7 and C_{12} methylene protons of 1-substituted DHP's.[9] Although the coalescence temperatures of the two sets of protons differ, the similar ΔF^* values arise from ΔS^* values close to zero. Several important conclusions can be drawn from Lansbury's work.

First of all, inversion barriers for most simple dihydropleiadene derivatives were too low to permit isolation of atropisomers. 7-Isopropylidene-DHP (5), however, should be resolvable, since the magnetic nonequivalence of the methylene protons was still evident at 200°. This requires a $\Delta F^* > 20$ and an inversion rate < 74 sec^{-1}.[7] In support of this low inversion rate, these workers reported the isolation of optically active 5. The vinyl methyl groups of 5 clearly increase the energy of the transition state for inversion, since 7-methylene-DHP, which lacks these vinyl methyls, is not resolvable (ΔF^*=15.2 kcal/mole).

Other C_7 substituent effects were also reported.[7] For example, 1,7,7-trimethyl-DHP,

in which the inversion barrier should be reduced due to CH_3-H steric interaction, inverted so rapidly that no methylene peak broadening was observed from +40 to -60°. A similar result could be expected for both trans-7,12-dimethoxy- and trans-7,12-diacetoxy-DHP. However, both compounds were reported to have enhanced free energies of activation (ΔF^*=14.3 and 15.2 kcal/mole, respectively) in comparison to DHP itself (ΔF^*=13.6). Lansbury and co-workers attributed the larger ΔF^* values to restricted rotation in the transition state.[7]

The inversion barrier of 7,7-d_2-DHP might be slightly increased if the ground state steric compression of the deuterated DHP is less. Deuterium isotope effects have been detected in biphenyls, for example, in which the steric interaction operates in the transition state.[10] Since the ΔF^* values of both the deuterated and the unlabeled DHP were found to be identical, it is possible that the nmr technique lacks the sensitivity required to detect isotope effects of $k_H/k_D \cong 1.2$.[7] In comparison to DHP, dihydrocyclohepta[de]naphthalene (6) showed no evidence of hindered inversion down to -60°.



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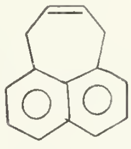

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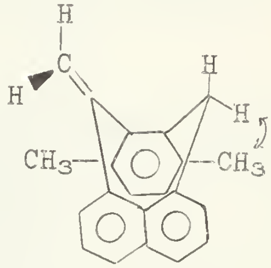

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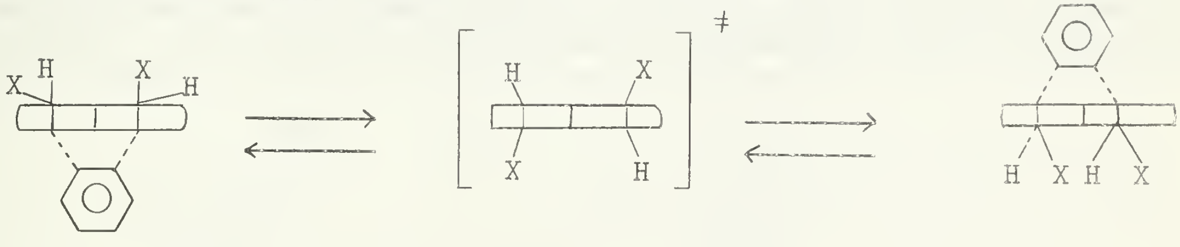
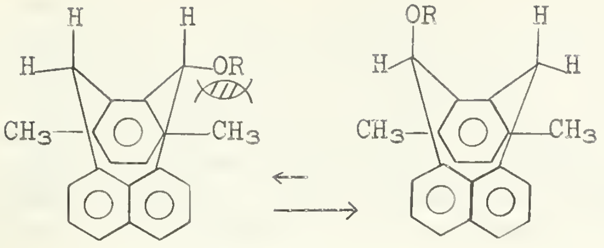
Other substituent effects have also been reported. Lansbury and Saeva have shown that the inversion rates of several DHP's with substituents of varying polarity at C_1 have no effect on ΔF^*. These results have been interpreted as showing that the steric effect of C_1 substituents is similar in both the ground and transition states.[9]

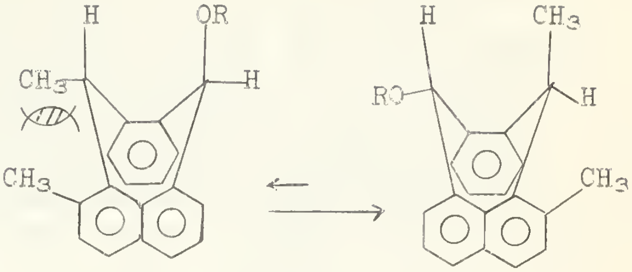
In contrast to the C_1 substituent results, C_8 and C_{11} substituents noticeably affect the inversion barrier.[7] The proximity of C_8 and C_{11} substituents to the C_7 and C_{12} substituents, respectively, is evident from studies of the nuclear Overhauser effects[11] on 7-methylene-8,11-dimethyl-DHP (7). Irradiation of the C_{11} methyl group produced a 16% increase in the intensity of the equatorial C_{12} proton. This intensity increase indicates that the methyl and the equatorial hydrogen dipoles are close enough for interaction.[12] The observation that 8-methyl-DHP has an intermediate value of 14.5 kcal mole for ΔF^* in comparison to DHP (13.6) and 8,11-dimethyl-DHP (15.6) has led Lansbury and co-workers to postulate a planar transition state for the inversion process.[7] The steric effect, which leads to increased strain in the transition state, causes a regular increase in ΔF^* upon the addition of methyl groups in the ortho position of the benzene ring.



Since inversion rates indicated that the conformers of the various DHP's could be "frozen," low temperature nmr spectra were used to determine conformational preferences.[13,14,33] In order to determine the conformational preferences of 7-methoxy- (8) and 7-acetoxy-DHP (9), Lansbury and co-workers compared the chemical shifts of the methyl, methylene and methine protons of 8 and 9 with those of dihydropleiadenes constrained to a particular conformation,[13] in the same manner as the t-butyl group has been used to constrain the cyclohexane ring.[15] The models (10 and 11) and their chemical shifts are shown below. Comparison of these results

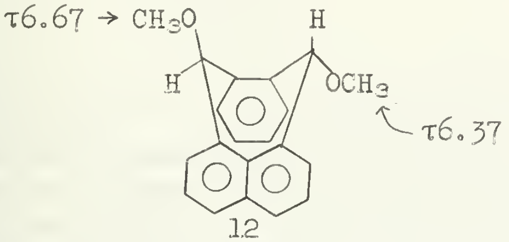


10 R=CH$_3$ τ6.65
R=Ac τ7.95



11 R=CH$_3$ τ6.38

with the nmr spectra of trans-7,12-dimethoxy-(12) and trans-7,12-diacetoxy-DHP (13), demonstrate that the equatorial methoxy (or acetoxy) group absorbs downfield from the axial group. With this data in mind and the fact that the nmr spectrum of



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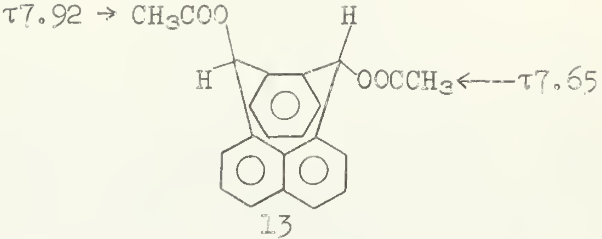

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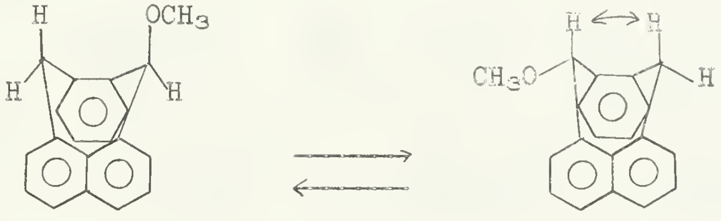
7-methoxy-DHP showed methyl absorptions at τ6.67 and τ6.37 (-20°) with the former (axial) being 2.2 to 2.5 times more intense, the free energy difference was calculated to be -0.41±0.1 kcal/mole in favor of the axial conformation. In the same manner, the axial acetate signal of 7-acetoxy-DHP was found to be 3.0 to 3.3 times more intense than the equatorial, corresponding to ΔF^{o}=-.55±0.1 kcal/mole.[13] The higher chemical shifts of the axial methoxy and acetoxy groups were expected, since such axial groups lie in the positive shielding region over the aryl rings.[16]

Surprisingly, however, the most intense methine signal (equatorial) was at higher field than the axial. In the AB quartet of the C$_{12}$ methylene protons, the high-field doublet is also the most intense and attributed by Lansbury and co-workers to the equatorial C$_{12}$ proton.[13] The low field (axial) methine and methylene signals were found to be broader than the high-field signals in accord with studies which demonstrate that the nmr signals of benzylic hydrogens perpendicular to a benzene ring are broadened by ortho and para long-range coupling.[17] In confirmation of this effect, Lansbury reported that simultaneous irradiation of the aryl proton region of 7-chloro-DHP, which exists entirely in the axial chlorine conformation, sharpened the axial C$_{12}$ doublet line width from 2.8 to 1.9 cps.[13] These nmr assignments have been further verified by the presence of nuclear Overhauser effects in certain conformations. In 7-methoxy-DHP, irradiation of the axial C$_{12}$ proton in 14b produced a 27% increase in the intensity of the axial C$_7$ proton, whereas irradiation of the axial C$_{12}$ proton of 14a produced no effect.[12]



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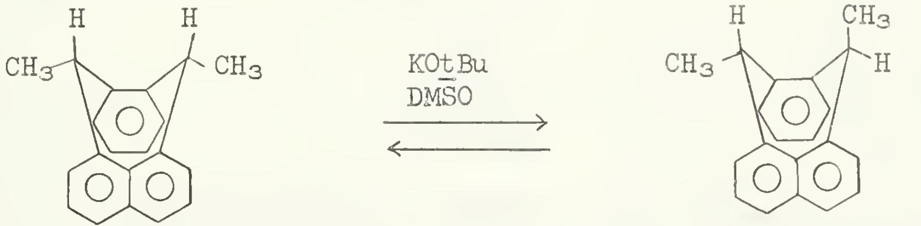
As additional evidence for the low-field axial proton, Lansbury and co-workers found that the low-field doublet of the AB spectrum of C$_{12}$ protons of 7-isopropylidene-DHP (5) completely disappeared and the high-field doublet became a sharp singlet with specific deuteration using potassium t-butoxide in the axial position,[13]

which is favored both on steric and stereoelectronic grounds.[18]

In addition to 7-methoxy-, 7-acetoxy- and 7-chloro-DHP, the conformations of 7-methyl-, 7-ethyl- and 7-isopropyl-DHP were determined in a similar manner.[14] Lansbury and Lacher determined the following ΔF° values for the equatorial $\rightleftharpoons$ axial equilibrium: 7-methyl-DHP (+1.0 kcal/mole); 7-ethyl-α,α-d_2-DHP (0.0 kcal/mole); 7-isopropyl-DHP ($<$ -1.5 kcal/mole). The equatorial preference for the C_7-methyl group was further demonstrated by base-catalyzed equilibration of cis- (15) and trans-7,12-dimethyl-DHP (16) from both directions. The difference between ΔF° values obtained by base catalysis ($\Delta F^\circ_{298} \simeq +0.4$ kcal/mole) and that obtained from 7-methyl-DHP ($\Delta F^\circ_{253} \simeq -1.0$ kcal/mole) is due to the entropy of mixing involved in the dl pair 16.[14] A determination of steric bulks in 7-substituted DHP's is complicated by steric interactions with the C_6, C_8 and C_{12} hydrogens. For example, 7-methyl-DHP shows a preference for the equatorial conformation in which steric compression with the C_{12} hydrogen is eliminated. Most other 7-substituted DHP's prefer the axial position probably because steric interaction with the C_{12} hydrogen is more easily avoided than interaction with the C_6 and C_8 hydrogens. The order of axial preferences (Cl, i-C_3H_7 > OAc $\gg$ OCH_3 > C_2H_5, H > CH_3) indicates that the relationship between the size of the substituent and its preferred conformation is indeed complicated.



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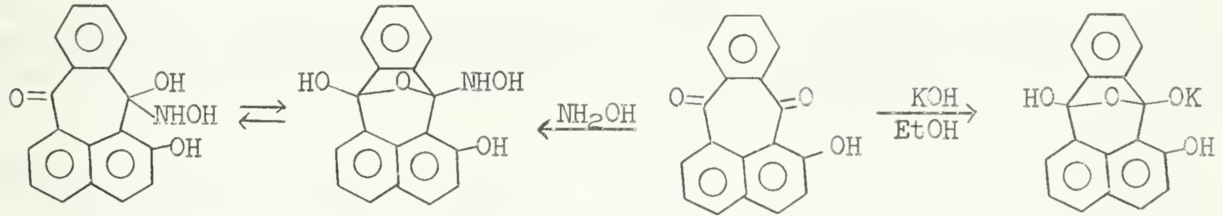
The non-planar nature of dihydropleiadenes has led to a consideration of transannular reactions due to the proximity of the C_7 and C_{12} carbon atoms.[19-22] In fact, such an interaction was postulated in 1933 by Fieser to explain both the formation of an unstable addition product of 1-hydroxy-7,12-pleiadione (17) with hydroxylamine and the enhanced solubility of 17 in alcoholic potassium hydroxide.[19]



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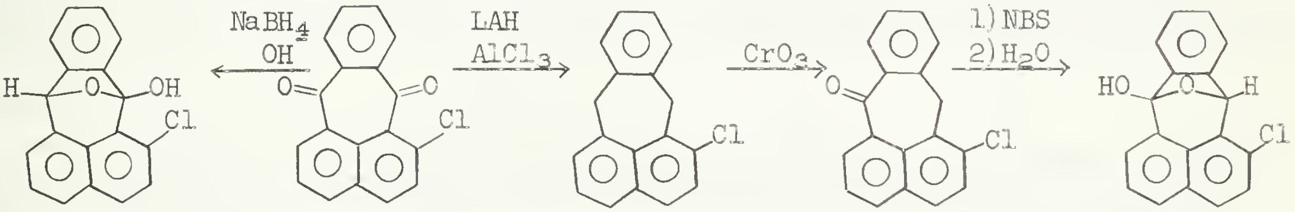
Such an interaction in the presence of base has recently been proposed by Lansbury and Saeva to explain the formation of the hemiketal (18) of 1-chloro-7-hydroxy-12(7H)-pleiadenone from the reduction of dione 19 with sodium borohydride in sodium hydroxide solution.[20] The structure of 18 was proven by synthesis of the other possible hemiketal (20).



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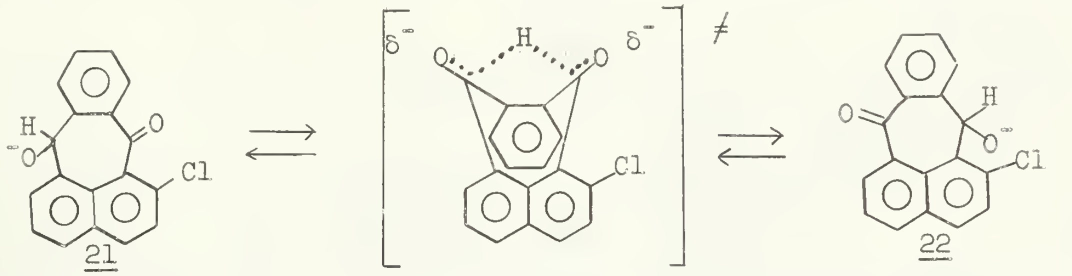
20

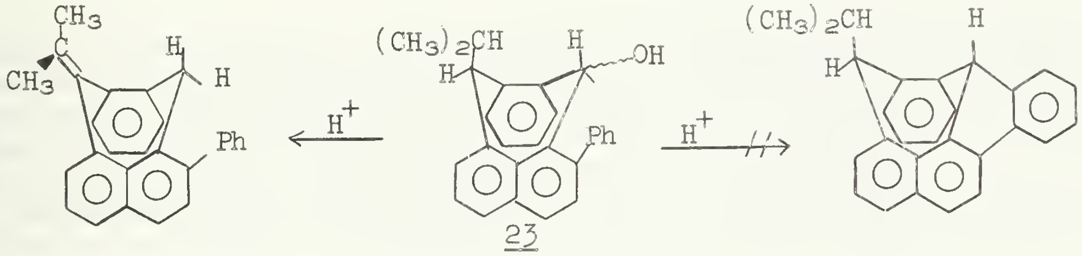
The tautomerism of both 18 and 20 was studied by nmr in both dioxane and dimethylsulfoxide. In comparison to 12-hydroxy-7(12H)-pleiadenone, which lacks the C_1 substituent and exists largely in the ketol form (K_{eq}=4.3) at 36°, the hemiketals 18 and 20 are favored over the ketol forms. In addition to the tautomerism study,

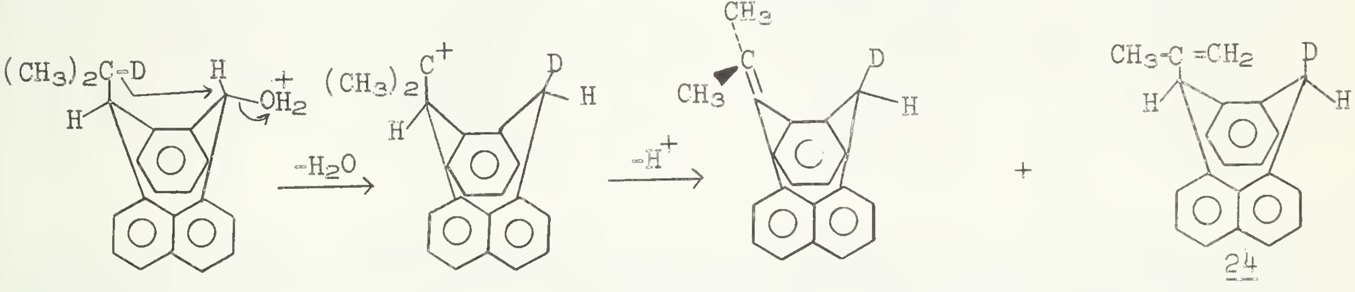
Lansbury and Saeva reported the rearrangement of 21 to 22 by alkali metal t-butoxide in dimethylsulfoxide.[20] The following activation parameters were calculated from duplicate runs at four temperatures with potassium t-butoxide as the base: $\Delta F^{\ddagger}_{21} \simeq 24.0$ kcal/mole; $\Delta H^{*} \simeq 24.5 \pm 1$ kcal/mole; $\Delta S^{*} \simeq -1+3$ eu. First-order kinetics were observed. The workers postulated a 1,4-hydride transfer mechanism, as shown below. This mechanism is supported by the observed kinetics and a deuterium labeling study using 7-d-21 with which there was no observable loss of deuterium in the rearrangement.



The ΔS* value was rationalized by a loosening of the solvent structure to compensate for the restricted mobility in the transition state.[20] Both relief of electrostatic repulsion of the carbonyl and chlorine dipoles and increased conjugation of the carbonyl with the aryl rings in 22 were offered as explanations for the driving force.

A transannular hydride shift has also been proposed by Lansbury and co-workers to explain the isopropylidene product in the attempted acid-catalyzed cyclization of 23. In this case a 1,5-hydride shift was postulated on the basis of the deuterium labeling studies shown below.[21] The minor product 24 was also detected. The stereospecificity of the labeling was demonstrated by nmr. The observation that 7-ethyl-12-hydroxy-DHP gave only small amounts of the rearranged product, while the 7-methyl compound gave none, was explained on the basis of the known order of carbonium ion stability: ter > sec > pri. The 1,4- and 1,5-hydride shifts demonstrate the proximity of the C_7 and C_{12} atoms.



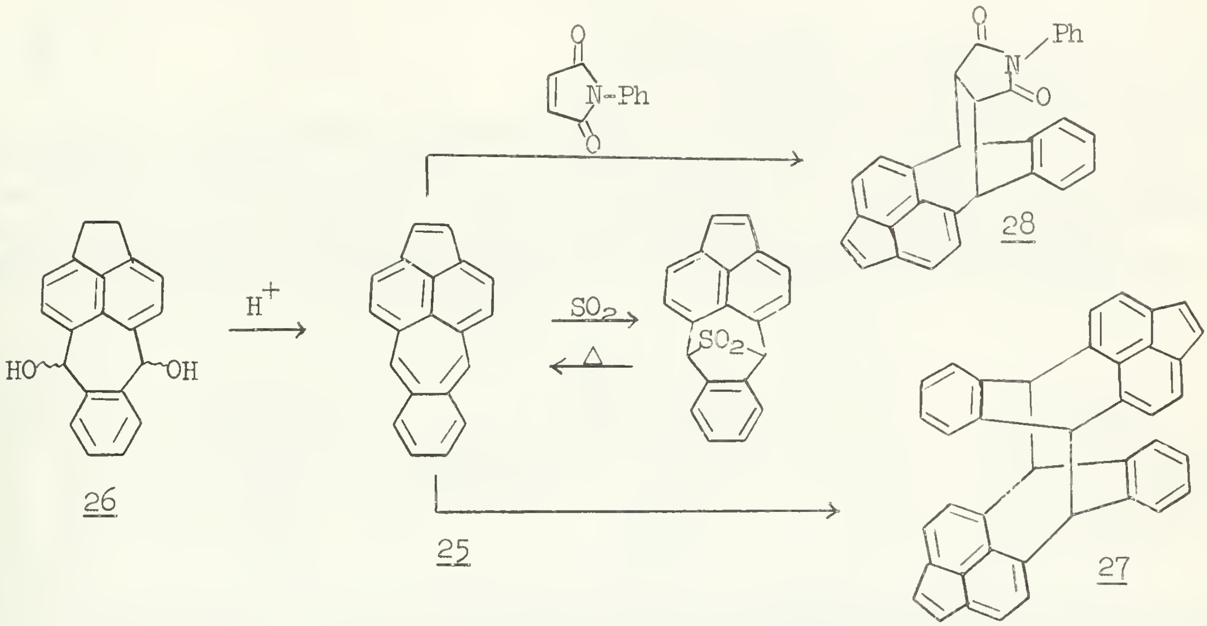


PLEIADENES

While the DHP derivatives have been known for many years, the planar "aromatic" pleiadenes have been considered as possible reaction intermediates[20,21] but have resisted synthesis until 1963 when Cava and Schlessinger reported the trapping of acepleiadylene (25).[5]

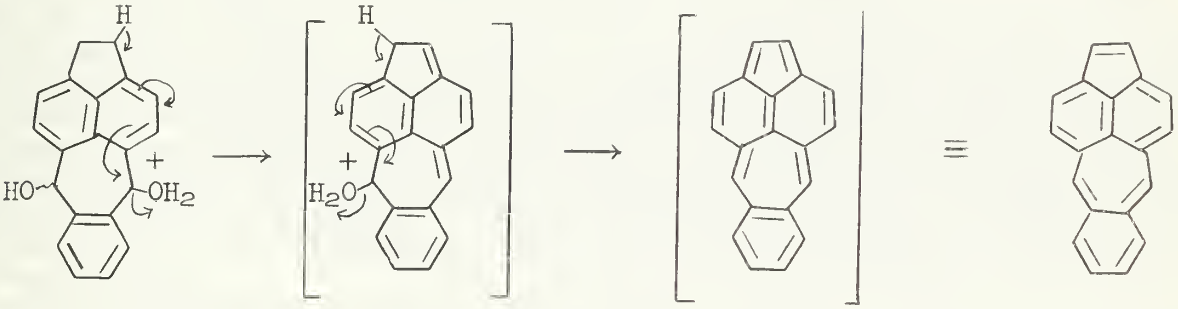
Treatment of 26 with either p-toluenesulfonyl chloride and pyridine or hydrochloric acid in a variety of solvents gave a deep blue solution which turned yellow over a forty-minute period.[23] A spectrum with eight maxima through the region 227 to 674 mμ was observed for a freshly prepared solution and was attributed to

acepleiadylene. Its dimeric and N-phenylmaleimide Diels-Alder products gave elemental analyses and ultraviolet spectra consistent with compounds 27 and 28, respectively. It should be noted that the formation of dimer 27 is a thermal $4+4$ cycloaddition reaction and is, therefore, not permitted to be a concerted process.[24] Polymeric products were also obtained. Both the dimer and N-phenylmaleimide adduct took up

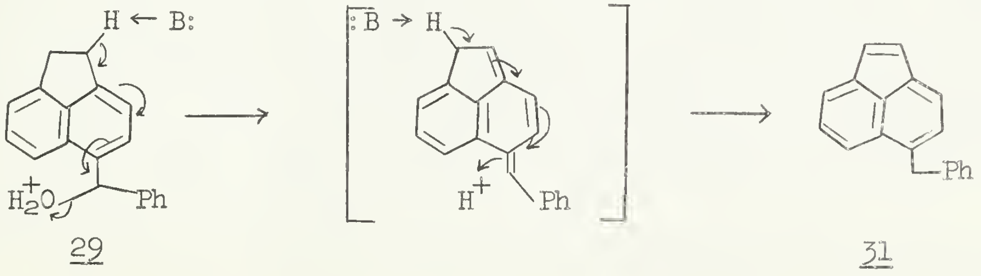


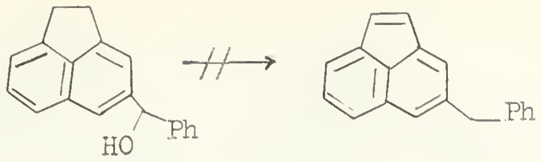
hydrogen to give products with uv spectra consistent with the presence of an acenaphthene chromophore.[23] Furthermore, the unstable acepleiadylene rapidly became yellow upon addition of sulfur dioxide. The blue color of the acepleiadylene could be regenerated by heating. This observation is consistent with addition of sulfur dioxide to o-quinonoid hydrocarbons to give sulfones.[25]

The mechanism of acepleiadylene formation was postulated by Cava and co-workers to involve two consecutive vinylogous elimination steps shown below.[26] In support



of this hypothesis, these workers found that although neither alcohol 29 or 30 was affected by dilute acid in dioxane, alcohol 29 reacted with p-toluenesulfonyl chloride in pyridine to give the elimination product 31, whereas 30 was stable under the reaction conditions. These results suggested to Cava and co-workers that





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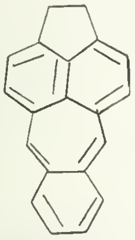
the formation of 31, as well as that of acepleiadylene, proceeded through a quinonoid intermediate rather than *via* a hydrogen transfer mechanism involving carbonium ions.[26] Such a quinonoid species cannot be formed from 30.

Acepleiadylene was found to be the most stable of the pleiadenes synthesized. Cava and his co-workers have prepared acepleiadene (32), as well as substituted pleiadenes (33-35) by several methods.[27-30] Of the methods tested, pyrolysis at $>$ 200° and photolysis of the corresponding sulfones were most effective for production of transient pleiadenes. In contrast to the sulfone of acepleiadylene, the sulfones of the other pleiadenes were easily isolated. An attempted formation of 34 by base-catalyzed elimination of hydrogen bromide from 1-methyl-7-bromo-DHP was unsuccessful.[28]



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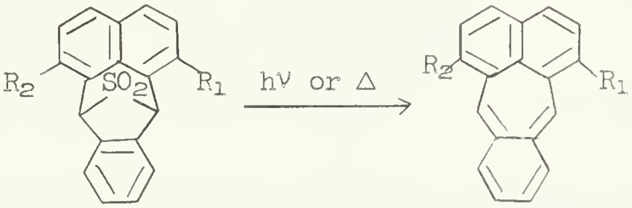


33, R_1=R_2=H

34, R_1=H; R_2=CH_3

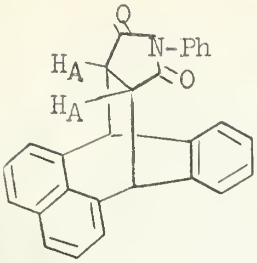
35, R_1=R_2=CH_3

It is interesting to note that while N-phenylmaleimide formed adducts with the various pleiadenes under pyrolysis conditions, no Diels-Alder products were isolated under photochemical conditions.[27,30] Cava and co-workers suggested that this difference is not due to generation of an energetically excited state of pleiadene under photolytic conditions. They proposed that at low temperatures the reaction with N-phenylmaleimide is too slow to compete with dimer formation, since the elimination of 7,12-dibromo-DHP with either zinc or copper at 25-150° also produced only dimer in the presence of N-phenylmaleimide.[30]

In the Diels-Alder reactions of pleiadene, bond formation at the carbons shown (36, 37) is reported to be favored over bonding at carbons 8 and 11 on the basis of molecular orbital calculations by the free electron method.[31] In order to distinguish between the *exo* (36) and the *endo* (37) isomers, Cava and Schlessinger have compared the chemical shift of the H_A protons of the pleiadene adduct (τ6.15) with that of the anthracene adduct 38 (τ6.57). On the basis of this nmr data, the *exo* stereochemistry, in which a larger deshielding effect was attributed to the naphthalene ring, was assigned.[30] Molecular models would seem to indicate, however, that the effect of the naphthalene ring may not differ appreciably from that of the benzene ring.

Cava and Schlessinger have proposed the *anti* structure 39 for the pleiadene dimer on the basis of the following evidence. The proximity of the aromatic rings is suggested by the ultraviolet spectrum in which absorption is shifted to higher wavelengths. The carbon-hydrogen analysis and an osmometric molecular weight determination are consistent with the proposed structure. The nmr spectrum shows a sharp singlet of four protons at τ3.22, as well as a four protons singlet at τ4.38 and a sixteen proton multiplet between τ2.3-2.7.[30] The *syn* isomer (40) was ruled out since it should absorb at higher field, as in β-heptacyclene, 41, (τ2.6-3.0) because of the shielding effect of aryl groups, which lie closely over each other. The sharp singlet at τ3.22 was attributed to the *para* (H_B) protons which lie in the shielding region over the benzene ring.[30] The absorption of these four H_B protons to give a sharp singlet would seem unlikely, since spin-spin coupling with the adjacent protons should produce at least a doublet (J=6-9 cps).

The reactivity of the pleiadenes prepared by Cava and co-workers is in sharp contrast to the stable nature of cyclohepta[de]naphthalene derivatives (2, 42, 43), which have been isolated as red crystals.[2,3] The results of Cava's group demonstrate that the *o*-quinodimethane moiety of the pleiadenes influences their stability and,



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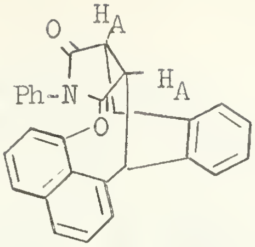

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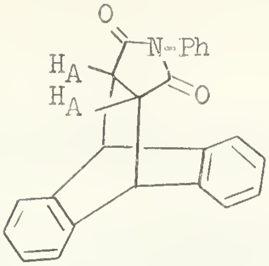

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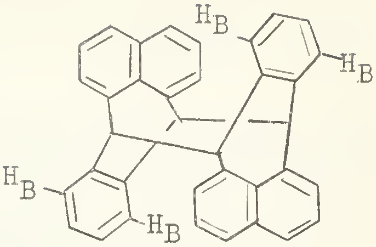

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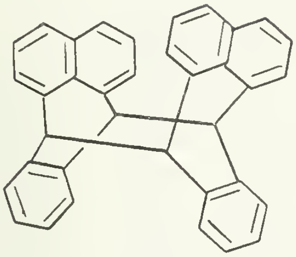

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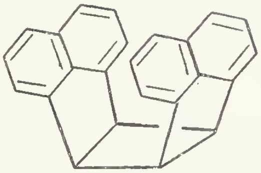

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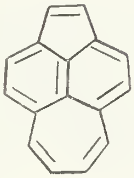

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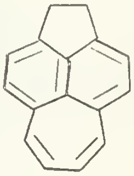

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consequently, the ease with which they undergo dimer formation and Diels-Alder additions. Although the reactivity of pleiadenes and cyclohepta[de]naphthalenes differs greatly, in both systems the hydrocarbons containing a acenaphthylene moiety, 25 and 42, respectively, are the most stable. Moreover, at first glance this increase in stability is in apparent disagreement with Hückel's 4n+2 rule, since acepleiadylene (25) and cyclohepta[de]acenaphthylene (42) contain 20 and 16π electrons, respectively, in comparison to pleiadene (33) and cyclohepta[de]naphthalene (2) with 18 and 14π electrons, respectively. This apparent discrepancy has been resolved[2,17] by attributing a more dominant role in the resonance stabilization to the peripheral π electrons, in accord with Platt's theory.[32]

CONCLUSION

Although cyclohepta[de]naphthalenes can be isolated as stable compounds, pleiadenes have been synthesized only as short-lived intermediates which lead to the formation of polymers, dimers and Diels-Alder products. On the other hand, the dihydropleiadenes are stable, non-planar molecules which have been investigated with respect to their inversion rates, conformational preferences and transannular reactions, in addition to their ability to serve as pleiadene precursors.

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RECENT STUDIES ON HINDERED ROTATION IN AMIDES

Reported by Steven D. Beare

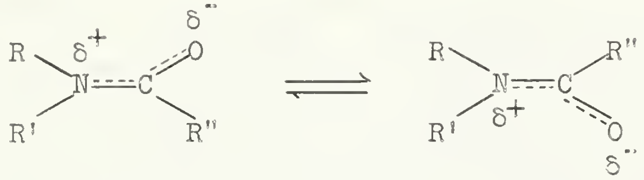
October 30, 1967

INTRODUCTION

The general phenomenon of restricted rotation about single bonds containing partial double bond character has been observed for some time.[1,2] Examples of compounds exhibiting such mesomorphism are nitrosoamines, alkyl nitrites, carbamates, hydrazines, hydrazones, boranes, and amides. Nuclear magnetic resonance spectroscopy has played a key role in the detection and elucidation of hindered rotation, and this seminar will discuss its application in recent studies on hindered rotation in amides.

ACTIVATION PARAMETERS

Restricted rotation about partial double bonds was first predicted by Pauling[3] for the carbonyl-nitrogen bond of amides due to the possibility of planar delocalized structures 1a and 1b.



1a 1b

Phillips,[4] and Gutowsky and Holm[5] confirmed this postulate with the classical observation that the nmr spectrum of N,N-dimethylformamide (DMF) displays two N-methyl signals at room temperature, which gradually broaden and then coalesce into a sharp resonance upon increasing the temperature to 100°C. This coalescence at higher temperatures was interpreted as rapid rotation about the nitrogen-carbonyl bond,[5] thus indicating that the reorientations could be treated as a typical rate process, with their temperature depenience following the familiar Arrhenius equation: $k_{exchange} = Ae^{-Ea/RT}$. Ea is the activation energy required to overcome the barrier to rotation while A is the frequency factor. The exchange rate k can be obtained from a line-shape analysis, since the resonance line-shapes and separations are dependent upon the average lifetime (1/k) an exchanging nucleus spends in each site. From an Arrhenius plot, Gutowsky and Holm obtained barrier heights of 7 ± 3 kcal/mole and 12 ± 2 kcal/mole for DMF and dimethylacetamide (DMA), with frequency factors of 10^3-10^7 and 10^7-10^{10} respectively.

A third activation parameter which may be gleaned from rate studies is the free energy of activation, $\Delta G^{\ddagger}_T$, evaluated from the Eyring equation in the form $\Delta G^{\ddagger} = -RT \ln(k_{exchange}\ h/kT)$, where k is Boltzmann's constant and h is Planck's constant. Gutowsky and Holm obtained a $\Delta G^{\ddagger}$ at 372°K of 22 kcal/mole for DMF, which they felt was in good agreement with Pauling's estimate of 21 kcal/mole[3] for the resonance stabilization of the planar amide group by double bond contribution.

However, if the resonance energy of the amide group is compared to the more related enthalpy term, where $\Delta H^{\ddagger}_T = Ea - RT = 6.4$ kcal/mole at 298°K, poor agreement is obtained. This large discrepency is not serious, as more refined determinations[6] of activation parameters for DMF have yielded an activation energy on the order of 22-27 kcal/mole.

As an illustration of the experimental errors in obtaining rates from fast exchange studies by nmr, Table I lists activation parameters for DMF measured by various workers using different levels of sophistication.

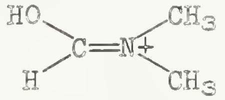
This wide range of activation parameters for just one amide would appear to make comparisons with other amides somewhat tenuous.

Table 1 Activation Parameters for Hindered Rotation in DMF

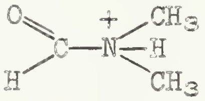
Frequency ~~Magnetic field~~ M(H_z)	Ea(kcal/mole)	Log frequency factor	$\Delta G^{\ddagger}_{298^oK}$(kcal/mole)	Method (ref.)
17.735	7 ± 3	3-7	21.0	a(5)
60	9.6 ± 1.5	6.5	23.1	b(7)
60	18.3 ± .7	10.8 ± .4	21.0	c(8)
60	26	16	21.6	b(9)
100	22	13	21.7	d(6)
60	27.4	16	23.0	e(6)

a peak-separation (uncorrected for coupling)
b intensity-ratio (corrected for coupling)
c intensity-ratio (uncorrected for coupling)
d total line-shape analysis (nuclear magnetic double resonance eliminated coupling)
e $DCONMe_2$-line-shape (coupling negligible)

Whittaker and Siegel[10] observed that Ea for DMF could be affected by up to 7 kcal/mole depending on the solvent used. From similar observations in a study on hindered rotation in carbamates, Lustig[11] has recently concluded that in this system calculations of activation parameters are of questionable meaning, since corrections of unknown magnitude are necessary due to self-association in the neat compound or solvent association upon dilution. In a more positive vein, Conti and von Philipsborn[9] recently redetermined activation parameters for DMF (Table 1) with high confidence limits, concluding that the often quoted[1,2] activation energy of less than 20 kcal/mole for this amide is too low. These workers used monodeuterated d-DMF in order to remove long range spin-spin coupling with the formyl proton ($J_{\underline{trans}}$ = 0.65 H_z and $J_{\underline{cis}}$ = 0.3 H_z), since Fraenkel and Franconi[7] had demonstrated that Ea obtained by neglecting the two spin couplings is too low by ca. 1 kcal/mole. In addition these workers[7] had observed by nmr that in 100% H_2SO_4 DMF has a higher Ea by 3 kcal/mole (Tc = 130°) as a result of strengthened C-N double bond character from O-protonation, 2a, while in aq.5N HCl DMF appears to protonate on nitrogen, 2b, as evidenced by a low Tc = 43°. In apparent contradiction, Conti and von Philipsborn[9] found comparable activation parameters for DMF and d-DMF in trifluoroacetic acid, concluding that compensation effects in this acid might be operative whereby in TFA protonation occurs on both oxygen 2a and nitrogen 2b. However, it seems more likely that the sensitivity of the nmr method is insufficient to rule out exclusive N- or O-protonation on the sole basis of activation parameters.



2a



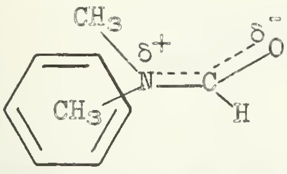
2b

The recent use of spin-echo methods by Allerhand and Gutowsky[12] allows measurement of faster exchange rates than the nmr steady state method, thereby encompassing a wider temperature range. The primary difference in activation parameters by the two methods was seen for frequency factors. For example, an earlier nmr study by Rogers and Woodbrey[8] indicated a value of 10^9 for N,N-dimethyltrichloroacetamide while the spin-echo studies yielded 5 x 10^{12}, in better agreement with the predicted value of 10^{12}-10^{14} for a pseudo first order activation process proceeding by bimolecular collisions.[12]

Table 1 also indicates that reasonable frequency factors are obtained as increasing care is taken in carrying out the kinetic experiments and analyzing the results, while $\Delta G^{\ddagger}$ has remained essentially constant. In a thorough error analysis Gutowsky has suggested[13] that the free energy of activation is the parameter least susceptible to systematic errors, and evidence will be presented later in this seminar for a good correlation between activation parameters determined by nmr and more conventional methods.

ISOMER ASSIGNMENTS

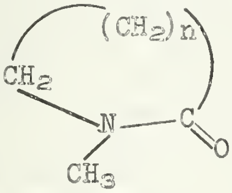
Since restricted rotation in symmetrically disubstituted amides involves two isomers which are indistinguishable by non-nmr methods, isomer assignments have been of some controversy. Analogous to substituted ethylenes, where $J_{trans} > J_{cis}$,[14] the separate N-methyl resonances of DMF and DMA have been assigned as either cis or trans (with respect to the carbonyl oxygen in this seminar) by comparing the relative magnitudes of their coupling constants with the formyl proton[15] or acetyl methyl protons.[16] In the case of N,N-dimethylbenzamide, where no long range coupling is observed, assignments have been made by a comparison of unequal upfield methyl shifts in aromatic solvents with similar shifts in amides where the configurations are known. Hatton and Richards studied solvent shifts of DMF in benzene[17] using cyclohexane as an internal standard, so that chemical shifts of cis and trans methyls represented a specific interaction between the benzene ring and the amide molecule. They found that upon increasing dilution with benzene the methyl trans to the carbonyl moved much further upfield than the cis methyl, suggesting collision complex 3 between the amide and benzene molecules, with the positively charged nitrogen close to the high π-electron density of the benzene ring.



3

Evidence in support of this model was obtained from infrared studies, which showed the carbonyl stretching frequency was unperturbed for a series of amides in going from benzene to carbon tetrachloride, while the N-H stretch of N-methyl acetamide was lower in benzene than in carbon tetrachloride.[18] Regardless of how accurate this model may be, isomer assignments by induced solvent shifts are not independent of those based on coupling constant assignments, which indicate that the cis methyl protons in DMF and DMA[19] are more shielded than the lower field trans methyls. However, the magnetic nonequivalence of geminal methyls in amides is generally attributed to the magnetic anisotropy of the carbonyl group,[8,16] which should provide a deshielding effect on the cis methyl according to studies on formaldehyde.[20]

Drago and coworkers[21] recently verified the coupling constant based assignments by a comparison of nmr contact shifts of amides and lactams in paramagnetic Nickel (II) complexes with the shifts of the uncomplexed compounds. They found that in a series of complexed N-substituted lactams 4, n = 2,3,4 the N-methyl, which must be cis to the carbonyl,[22] exhibits a much smaller downfield shift than does the N-methylene relative to the uncomplexed lactams. Complexed DMF and DMA both show one N-methyl which undergoes a smaller downfield shift than the other relative to the uncomplexed amides. By adding excess amide and following each methyl resonance back to uncomplexed amide, the higher field resonance for both DMF and DMA was shown to be the cis methyl, the same conclusion arrived at by coupling constant considerations.[15]



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The conflict between theoretical deshielding and experimental shielding of the cis methyl may lie in the validity of the model for the shielding (+) and deshielding (-) regions of the carbonyl group (Fig. 1). For example, Karabatsos and coworkers[23] observed that in a series of aldehydes (5) where the rotameric populations are known, when H_A is eclipsed with the carbonyl group it resonates at higher field than staggered H_B. A model (Fig. 2) based on recent values[24] of the three principal

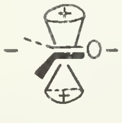
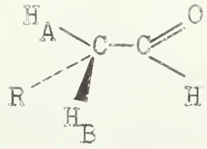


Fig. 1



5 R=alkyl

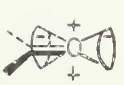
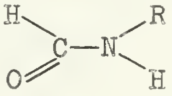


Fig. 2

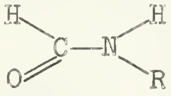
magnetic susceptibilities of the carbonyl bond was proposed which qualitatively agreed with experimental results although quantitative agreement was poor.

CIS-TRANS ISOMERISM

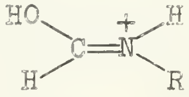
When the nitrogen atom in amides is unsymmetrically substituted, the possibility of *cis-trans* isomerism exists. Earlier work indicated that N-methylamides exist predominantly or solely in one configuration, or undergo rapid rotation about the C-N bond.[4,5] Later, more extensive work by LaPlanche and Rogers showed the presence of 8-18% of the minor *trans* isomer (alkyl group *trans* to the carbonyl) in a series of N-alkylformamides, but only one isomer was detected for the corresponding N-alkylacetamides,[25] assigned the *cis* configuration from infrared studies.[26] A similar nmr study[27] of disubstituted amides showed that in formamides, the bulkier group tends to be *trans* to the carbonyl, while in acetamides it is *cis* to the carbonyl, consistent with the greater van der Waals radius of methyl (2.0 Å) as compared with carbonyl (1.4 Å) and hydrogen (1.2 Å).[28] Although LaPlanche and Rogers[25] observed that the percent of the minor *trans* isomer in N-alkylformamides (6a) increased as the alkyl group was made larger (8% for $R=CH_3$ and 18% for R=*t*-butyl), rationalized by increased steric interactions between the alkyl group and the carbonyl oxygen in 6b, no explanation was offered for the greater stability of the more hindered 6b. A reasonable parallel may be drawn to aldehydes, where it is well known[29] that in propionaldehyde the methyl group eclipses the carbonyl group in the most stable conformation, presumably due to a combination of 1) favorable dipolar attractions, 2) possibility for internal hydrogen bonding, and 3) a distance whereby the methyl and carbonyl groups are in the attractive portion of the van der Waals potential energy curve.[29]



6a



6b



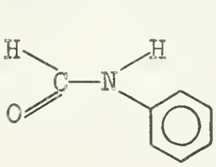
7

Mizushima[28] had earlier suggested from infrared studies that formamides, which strongly associate in solution, might derive greater stability from linear chains of 6b than cyclic dimers of 6a. This is consistent with the observation[25] that the isomer ratio for N-*t*-butylformamide increased from 18% in benzene to 63% in 100% H_2SO_4, where O-protonation rather than N-protonation is known[7] to occur to give 7. In acid, specific associations of 6a and 6b would be broken down, resulting in a predominance of the thermodynamically favored isomer.

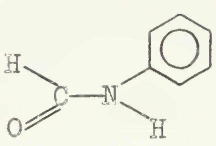
Recently, Barker and Boudreaux[30] detected 3% of the minor isomer of N-methylacetamide at 35° in aqueous solution, which was assigned to the *trans* configuration by its 0.17 ppm lower field N-methyl absorption than the *cis* isomer.[17,21,27] The separate N-Me resonances coalesced upon heating to 50°C, indicating a relatively small barrier to rotation. However, activation parameters were not calculated, presumably because a line shape analysis of two exchanging sites becomes complex as the relative population difference increases.[5,8]

Except for secondary formamides, then, it appears general that the less sterically hindered isomer predominates in mono- and di-alkylsubstituted amides.

A similar situation appears to exist for anilides, 8.



8a



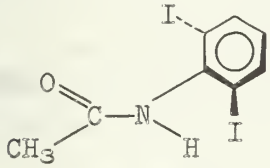
8b

For example, Randall and coworkers[31] found that the sterically favored *trans* isomer of formanilide 8b predominates only at less than 4% concentrations in $CDCl_3$. This is consistent with solute-solute associations at higher concentrations determining isomer stability. Assignments were based on coupling constants between the

formyl and N-H protons (J_{trans} = 11 H_z, J_{cis} = 2 H_z), which agreed well with those previously assigned to N^{15} formamide (J_{trans} = 12.9 H_z, J_{cis} = 2.1 H_z).[32]

Rae[33] attempted to determine the degree of coplanarity of the benzene ring and the amide group in formanilide by comparing the chemical shift of the formyl proton in 8b relative to that of the *trans* isomer in a number of 2,6-disubstituted formamides. Rae used Johnson and Bovey's[34] semiempirical model for the calculation of formyl proton shieldings by the benzene ring current,[35] concluding from observed formyl shifts that 2,6-disubstituted formanilides have an orthogonal relationship between phenyl and amide groups, while formanilide and 4-substituted formanilides are approximately planar molecules. However, due to the approximate nature of the ring current model by Johnson and Bovey[35] these results should only be interpreted as indicative.

Acetanilide has been shown in an x-ray study by Brown and Corbridge[36] to exist in the *cis* configuration (phenyl *cis* to the carbonyl). In a more refined x-ray analysis Brown[37] has recently shown that the phenyl ring is twisted out of the amide plane by 17.6°, indicating some steric repulsion between the phenyl and acetyl group. The *cis* configuration is retained in 2,6-diiodoacetanilide 9, although the bulky iodines force the phenyl ring to be orthogonal to the amide plane.[38]



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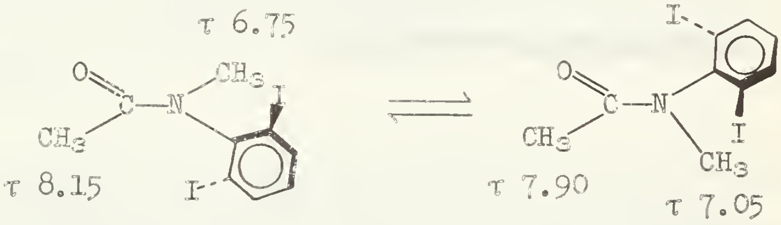
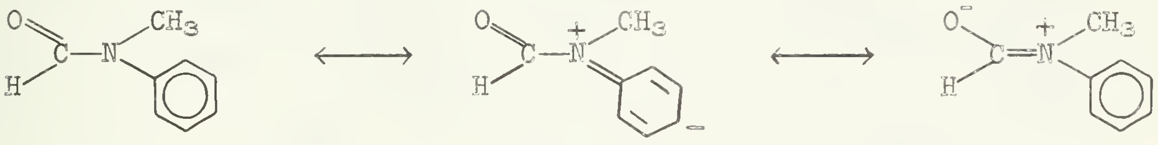


10a (*exo*) 10b (*endo*)

Upon N-alkylation of these anilides a reversal of structure is seen. Pedersen examined N-methylacetanilide and 2,6-diiodo-N-methylacetanilide by x-ray and nmr, concluding that both compounds existed in the *exo* configuration 10a in the solid state and in pyridine as well, where only 0.5% of the *endo* isomers 10b were detected.[38] In each of these compounds the phenyl ring and amido group are orthogonal, which would explain the isomer ratio in terms of steric interactions between methyls in 10b.

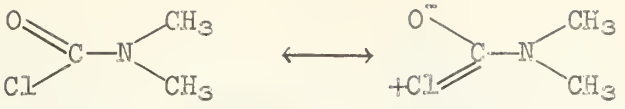
Randall and coworkers observed that N-methylformanilide exhibits *cis-trans* isomerism in benzene with an isomer ratio of 19:1.[39] The predominant isomer was assigned the *trans* configuration 11a by comparing methyl-formyl proton coupling constants with those of *cis* and *trans* N-methylformamide.[17] Such a conformation as 11a might be expected to lead to a lower barrier to rotation than for alkyl substituted amides depending on the importance of an additional resonance structure 11b relative to 11c. Although no activation parameters appear to have been reported for simple anilides, Gehring and Mosher[40] have determined an Ea for N-methyl-N-vinylformamide of 15.7 ± 2 kcal/mole, which was compared to a value of 28 ± 2 kcal/mole for DMF from the same nmr study.



11a 11b 11c

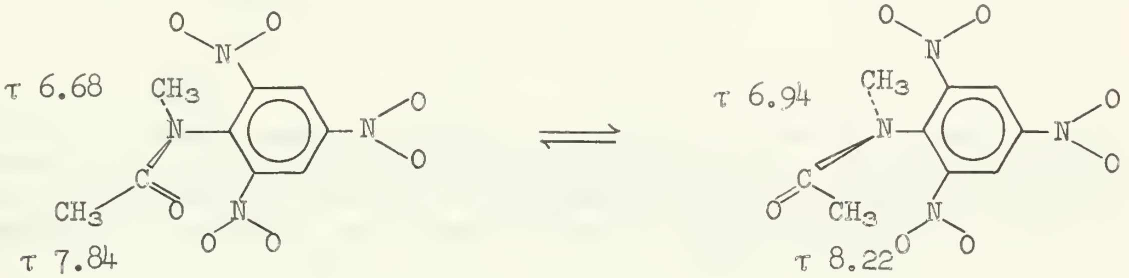
Neuman and coworkers[41] similarly found a relatively low Ea for N,N-dimethylcarbamoyl chloride 12a compared to DMF using a total line-shape analysis. The value of 16.9 ± 0.5 kcal/mole, considered more accurate than earlier determinations[8,12] for 12a, was attributed to an additional canonical structure 12b.

Recently Weil and coworkers[42] determined activation parameters for N-acetyl-N-methyl-2,4,6-trinitroaniline 13 in perdeutero-1,4-dioxane, obtaining Ea = 19.7 ± .3 kcal/mole and log A = 14.0 ± .2. That unusual electronic effects are operating in



12a 12b

the polynitroaniline 13 is seen by comparing isomer ratios (13b/13a = 0.29 at room temperature) to 2,6-diiodo-N-methylacetanilide, where it may be recalled that the



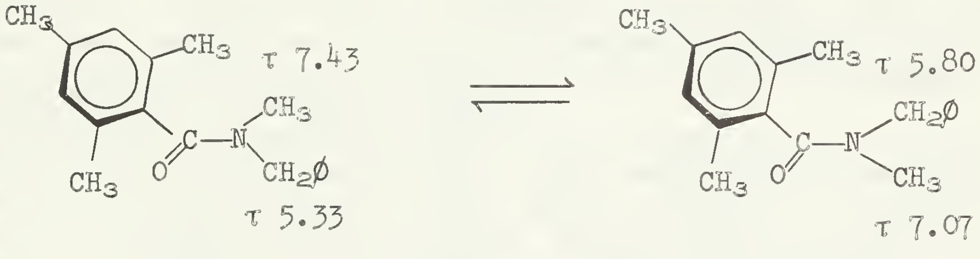
13a (endo) 13b (exo)

exo isomer 10a was found to predominate.[38] Weil attributed the increased stability of 13a to attraction between the carbonyl oxygen and the positive C$_1$ carbon atom of the trinitrophenyl ring, indicated by an increase in t[redacted] 13b with increasing temperature.

ISOLATION OF ROTATIONAL ISOMERS

If the barrier to restricted rotation about partial double bonds is unusually high, cis and trans isomers of unsymmetrically disubstituted amides should be isolable at room temperature. In principle, by the isolation of isomers one might compare the fast exchange rates (10-10^{6}sec^{-1}) obtained by nmr at high temperatures with slow rates at lower temperatures measured by conventional equilibrating techniques.

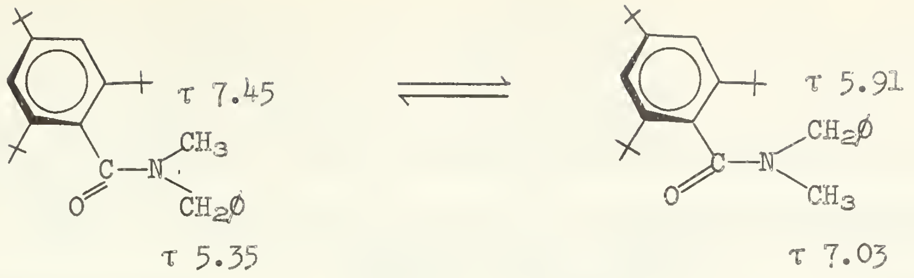
Mannschreck[43] reported the first isolation of rotational isomers, accomplished by further hindering rotation about the carbonyl-nitrogen bond in a benzamide with ortho substituents. The higher melting isomer of N-methyl-N-benzylmesitylenecarboxamide 14a was fractionally crystallized from the lower melting and less stable 14b.



14a 14b

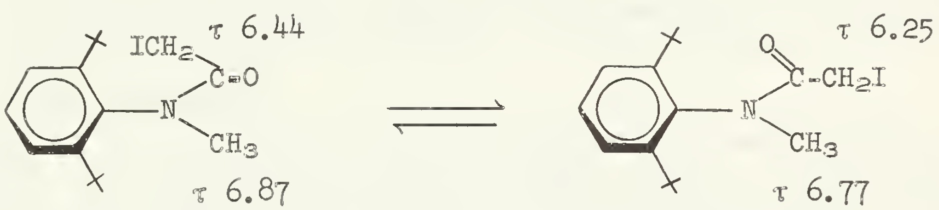
Isomer assignments were made by a comparison of N-alkyl solvent shifts in going from CCl$_4$ to benzene with similar shifts observed for analogous amides.[15,27] By isolating pure 14a and measuring the rate of formation of 14b by nmr in CCl$_4$ at 38°, Mannschreck calculated a $\Delta G^{\ddagger}$ of 22.9 kcal/mole.[43] Using this same principle, Staab and Lauer[44] separated the more hindered N-methyl-N-benzyl-2,4,6-tri-t-butylbenzamide 15, obtaining an even higher value of $\Delta G^{\ddagger}$ = 31 kcal mole^{-1} from equilibrations at 120° in 1-chloronaphthalene-benzotrichloride.

The equilibrium ratio of 15b to 15a was found to be 0.12, indicating a relatively high Gibb's free energy difference of 1.65 kcal/mole. Interestingly, the mass spectra of the two isomers indicated a preferential fragmentation of the C-N bond of 15b over that in 15a, with the relative intensities of the molecular ion peak at m/e 393-5 7.6% and 27.1% respectively.



15a 15b

In a more recent example, Chupp and Olin[45] were able to isolate the two isomers in a number of N-methyl-α-haloacetanilides and found an increasing barrier to rotation upon increasing the size of ortho-substituents, consistent with the results of Mannschreck[43] and Staab and Lauer.[44] For the ortho di-t-butyl-α-iodoacetanilide



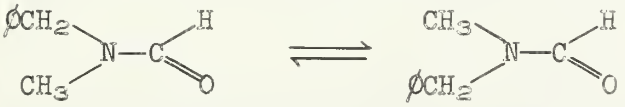
16a 16b

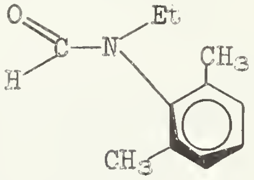
16, a $\Delta G^{\ddagger} = 29$ kcal mole^{-1} was determined by equilibrations at 111°C in CCl_4. An equilibrium constant of 0.15 was obtained with the predominant isomer being 16a, assigned by its upfield halomethyl shift of .2 ppm presumably due to shielding by the orthogonal phenyl ring.

In none of these three examples of isolable rotational isomers was it possible to compare the activation parameters obtained by equilibrating techniques with the fast exchange parameters, since no coalescence of isomer peaks was observed at temperatures available to nmr. In addition, suitable models for comparisons are somewhat tenuous due to the relative importance of substituent effects, pointed out by the Gibb's free energy difference between cis and trans isomers in 14-16 of .6-1.6 kcal/mole.

By selecting a compound which was amenable to both high temperature line-shape analysis and lower temperature equilibration methods, Gutowsky, Jonas, and Siddall[46] were able to show an excellent correlation between activation parameters obtained for the same compound in two independent ways.

N-methyl-N-benzyl formamide 17 exists in an isomer ratio of 17b:17a = 0.8 at ambient temperatures, but by complexing it with uranyl nitrate and stripping off the uranyl ion at low temperatures, an isomer ratio of 17b:17a = 1.6 is attained. This same method of enriching rotational isomers was previously described by Siddall[47] for N-ethyl-N-2,5-dimethylphenylformamide 18, which yielded an Ea = 26 ± 3 kcal mole^{-1}





17a 17b 18

by an equilibration study. However, no higher temperature line shape analysis was reported, possibly due to a high coalescence temperature. The Gibb's free energy difference between the two isomers of 18 of 1.3 kcal mole^{-1} makes comparisons[47] with activation parameters of DMF questionable.

Assignments of 17a and 17b were based on the relative line widths of the formyl resonances, where it may be recalled that $J_{trans} > J_{cis}$ in DMF.[15] The formyl proton

of 17a exhibited a peak width at half height of 1.9 H_z, while the less stable (by .135 kcal mole^{-1}) isomer 17b showed a narrower peak of 1.6 H_z. The return to equilibrium could be followed by the time dependence of the nmr spectrum from -2.5° to 25°C, while faster exchange rates were measured by a complete line shape analysis between 90° and 170° on both the benzyl and formyl protons (the methyl protons were not chemically shifted). The activation parameters obtained by the two methods are given in Table 2.[46]

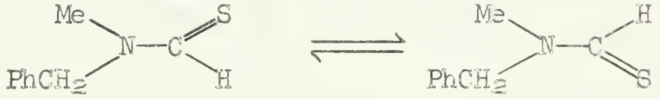
Table 2 Activation Parameters for N-methyl-N-benzylformamide

Activation Parameter	NMR Line-shape Analysis Benzyl	 Formyl	Equilibration Method
Ea(kcal/mole)	25.0±1.5	22.7±1.5	20.0±3
Log A	15.2±1	13.9±1	11.9±1.6
$\Delta G^{\ddagger}_{373°}$(kcal/mole)	20.9±0.4	21.0±0.4	21.6±0.7

A good fit between the two sets of data is observed, especially for free energies of activation, which as noted before, is the parameter least susceptible to systematic errors.[13] These results would appear to confirm the generality of Gutowsky and Holm's original theory[5] describing the effects of chemical exchange upon nmr spectra.

RESTRICTED ROTATION IN THIOAMIDES

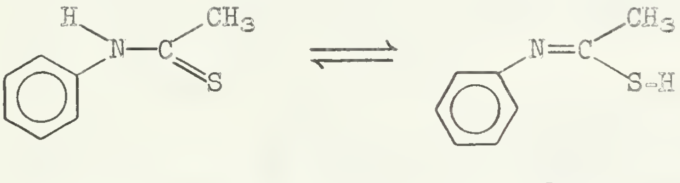
Interestingly, an earlier study by Walter, Maerten and Rose[48] showed the sulfur containing analog of 17, N-methyl-N-benzylthioformamide (19), to also exist in an equilibrium ratio close to unity (0.8), while the higher barrier to rotation in thioamides[49] allowed physical separation of the two isomers 19a and 19b. Assignments



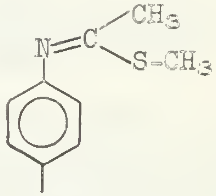
19a 19b

paralleled those by Gutowsky and coworkers for 17.[46] Nmr equilibration studies yielded an Ea = 25.14 ± .5 kcal/mole, about 5 kcal/mole greater than the corresponding amide (Table 2). The higher barrier to rotation in thioamides compared to amides has been attributed[19,41,49] to the increased polarity of the thioamide system as a result of less effective overlap of the lone-pair electrons in the 3p orbital of sulfur with carbon compared to the 2p orbital of oxygen.[50] For example, an activation energy of 28 kcal/mole was observed for N,N-dimethylthioformamide,[51] which is to be compared to 22-27 kcal/mole for DMF (Table 1). Similar differences are observed between other amides and thioamides.[41]

Earlier workers[52] had ascribed the presence of two isomers in the nmr of 20 to a thioamide-thioimidic acid tautomerism 20 ⇌ 21.



20 21



22

Rae[53] recently demonstrated that tautomerism was not the observed process by synthesizing methyl-N-p-tolylthioacetimidate 22, the nmr of which showed aromatic protons shifted to higher field by almost .6 ppm than the corresponding thioamide. Rae studied the change in the isomer ratio as the thiocarbonyl substituent of 4'-methylthioanilides was varied, finding behavior consistent with that observed in amides where the bulkier groups tend to be trans to one another in the most stable conformation.

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MECHANISM OF THE NITRAMINE REARRANGEMENT

Reported by Thomas R. Keenan November 2, 1967

INTRODUCTION

Many N-substituted aryl amines undergo acid catalysed rearrangement to form aryl-substituted products as shown in Figure 1. Most of these rearrangements involve initial N-X bond cleavage followed by intermolecular reaction to give rearranged products. Two notable exceptions to this rule are found in the nitramine ($X = NO_2$) and benzidine (X = NHPh) rearrangements which appear to proceed intramolecularly.[1,2]

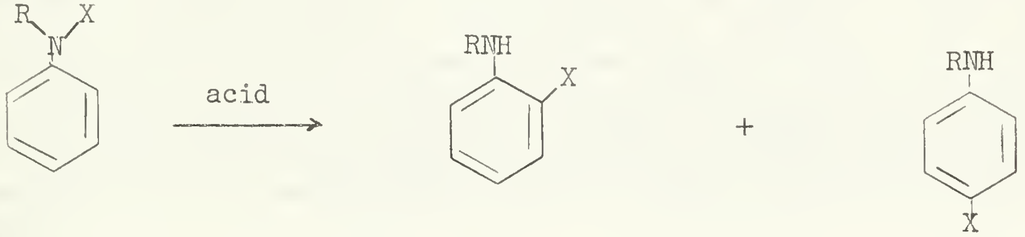


Figure 1. R = alkyl, H; X = halogen, alkyl, NO_2, NO, OH, NHPh.

DETERMINATION OF INTRAMOLECULARITY

Various criteria to distinguish experimentally between inter- and intramolecular mechanisms in such rearrangements have been applied. Dewar has suggested[3] that intramolecular rearrangement which proceeds via an ortho linked intermediate would be expected to give a large ortho/para ratio of products compared to the low ratio characteristic of electrophilic substitution in aniline by NO_2^+. This criterion would not be valid, however, if fission of the N-X bond gave rise to a migrating species which was different from NO_2^+ and, hence, would not necessarily give the same product ratios.[4] Alternatively, a reaction run in an isotopically labelled medium in which the migrating species would equilibrate with labelled material would give labelled products in an intermolecular process whereas isotopically normal products would result from an intramolecular pathway.[5] This criterion would distinguish an intramolecular mechanism from rearrangements where the migrating group is "free" to interact with the medium but would give incorrect results for processes in which one substrate molecule transfers its X-group to another. This possibility could be checked in two ways. Examination of the products of a simultaneous rearrangement of two compounds, which have comparable rates of reaction but one of which contains an isotopically labelled X-group, would rule out this process if no cross products were observed. Also, the observation that the rate of rearrangement is second-order in substrate would suggest that one molecule is transferring its X-group to another in an intermolecular process.

THE NITRAMINE REARRANGEMENT

The acid catalysed rearrangement of N-nitroaniline to o- and p-nitroanilines appears to be intramolecular over a wide range of acidities.[5-7] The ortho/para product ratio is significantly different from that obtained from nitration of aniline (Table 1) and no m-nitroaniline is produced in the rearrangement. Rearrangements carried out in the presence of ^{15}N nitric acid failed to give ^{15}N enriched products and cross products are generally not observed. Dewar has suggested[3] that even the existence of cross products would not rule out an intramolecular mechanism since it is possible that in intermediate which contains a migrating nitro-group could be partitioned between intermolecular reaction with another reactive species and intramolecular decomposition to products. The percent of intermolecular reaction would have to be small, however, for it to be meaningful to state that the rearrangement proceeds by an intramolecular pathway while the intermolecular component of the reaction leads to cross products. The rate of formation of products in the nitramine rearrangement is first order in substrate when a large excess of acid is used but is negligible in the absence of acid.[7]

	Isomer %		
	ortho	meta	para
Rearrangement of $PhNHNO_2$	93	0	7
Nitration of $PhNH_2$	6	34	59

Table 1. Proportions of isomers formed by rearrangement of N-nitroaniline and by nitration of aniline in 85% sulfuric acid at 10°.[1,5]

The existence of para-nitro products and the observed intramolecularity of the reaction impose formidable geometric requirements on the mechanism of rearrangement. Three major types of mechanisms have been suggested to account for these observations. Dewar has proposed[3] that the rearrangement proceeds via a π-complex intermediate. Hughes and Banthorpe and their co-workers[5-9] suggested that the reaction involves a Claisen type (or cartwheel) rearrangement of ortho- and para-linked C-nitrites. White and co-workers[4,10,11] have proposed that the reaction involves a radical pair which collapses to rearrangement products before either species can escape from the solvent cage.

π-COMPLEX MECHANISM[3]

According to the π-complex theory, a positive moiety can be held to an unsaturated substrate by a dative bond formed by electrons occupying delocalized π orbitals. This bond is expected to be of comparable strength to a normal covalent bond. Thus, the isomerization of the conjugate acid ($ArXH^+$) to a π-complex ($ArH \rightarrow X^+$) should require very little energy. As it is applied to the nitramine rearrangement, the π-complex theory predicts that a migrating nitronium ion (NO_2^+) "...should be able to rove freely over the π electron cloud, the latter providing a kind of electronic railroad over which X (NO_2^+) can move from one part of the molecule to another without ever being detached from the parent aromatic ring."[3] The preference of the migrating species for any position in the ring will be determined by the π electron density at that point and by the relative stabilities of the possible "quasi-classical" benzenonium or cyclohexadieneimine ions which the intermediate may form (in the absence of steric effects). The available evidence[13-15] indicates[3] that benzenonium ions are slightly more stable than π-complex forms but that they have similar energies. Accounting for the directing influence of the amino group, the changes in potential energy during the rearrangement are probably as represented in Figure 2. If the loss of a proton from A to form the stable ortho rearrangement product is facile, the system will be stabilized and the migrating group will have little chance to get to the para position.

The π-complex mechanism explains the intramolecularity and the existence of para products in the nitramine rearrangement as well as the ortho/para ratio and the absence of meta products. In addition, it predicts that the N-N bond heterolysis will give nitronium ion (NO_2^+) as the migrating species.

CARTWHEEL MECHANISM[5-9]

Brownstein, Bunton and Hughes have suggested[6] that the geometric requirement for para migration can be met in another way (Figure 3). This mechanism involves the rearrangement of protonated starting material eventually to form an ortho C-nitrite cyclohexadieneimonium ion which then may rearrange to the stable ortho-substituted product or may rearrange further, in a manner analogous to the Claisen rearrangement via a strainless ring, to form a para C-nitrite intermediate which rearranges to para product. The mechanism of the rearrangement of C-nitrites to products seems to have been given little attention, however, beyond the statement that "...the incipient aniline molecule would be presented with an almost unsolvated developing electrophile in close contact...[and]...direct electrophilic ejection of hydrogen would be likely without the formality of a σ-linked Wheland intermediate...."[7] A mechanism of this type accounts for the observed acid catalysis and can explain the existence of para products as well as the ortho/para product ratio and the absence of meta products.

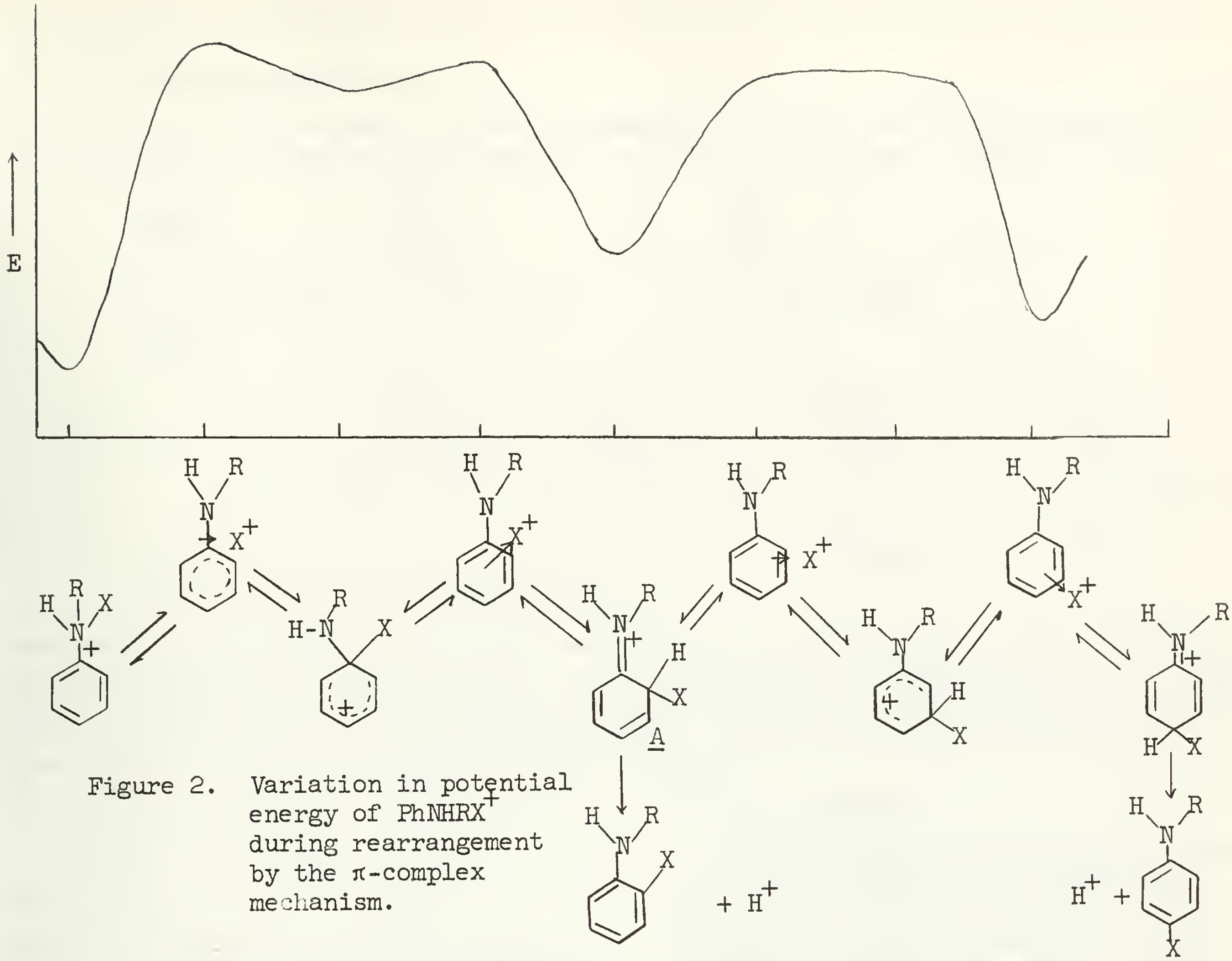


Figure 2. Variation in potential energy of $PhNHRX^+$ during rearrangement by the π-complex mechanism.

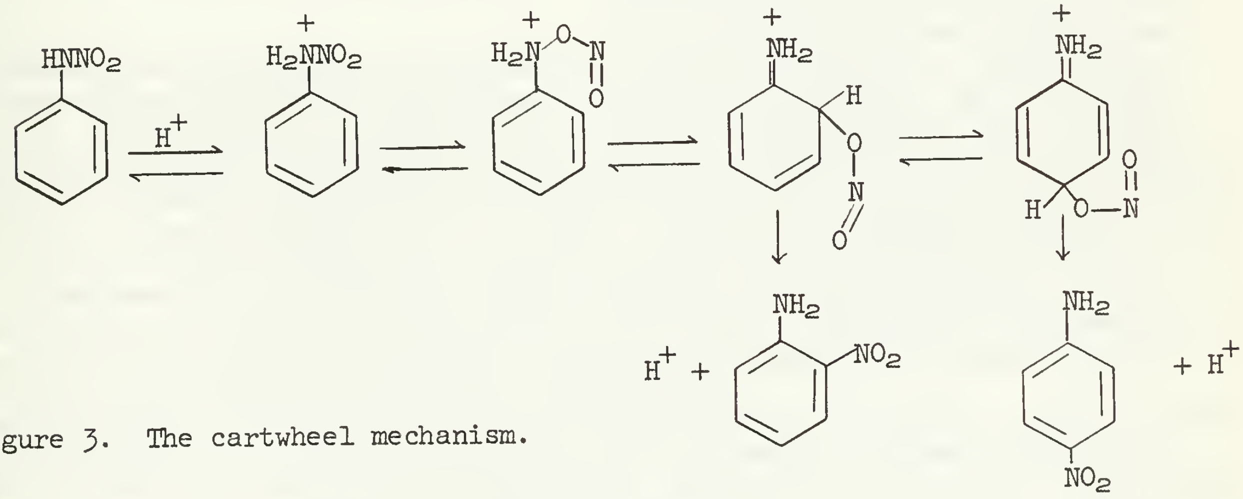


Figure 3. The cartwheel mechanism.

Some objection to the cartwheel mechanism has been raised[3,4,11] on the grounds that nitrite intermediates would be expected to undergo immediate hydrolysis to nitrous acid, nitrophenols, and phenylhydroxylamines under the reaction conditions in analogy to the reactions of alkyl nitrites. Proponents of the cartwheel mechanism argue,[7] however, that protonation and subsequent fission of the C-nitrite intermediates should not be particularly easy, because of positive charge repulsion, and because these intermediates would have a very facile alternative mode of decomposition to form rearrangement products. It may be significant that small amounts of nitrous

acid and other products which could come from C-nitrite hydrolysis are observed in these reactions.[4,7,9,11]

RADICAL PAIR MECHANISM[4,10,11]

A third mechanism which has been proposed for the nitramine rearrangement postulates homolytic cleavage of the N-N bond to form a radical pair (Figure 4) which undergoes multiple collisions before reaction in the solvent cage.[4] This mechanism is based mainly on the observation[4,10] that rearrangement of N-methyl-N-nitroaniline in 0.5 N hydrochloric acid gives appreciable quantities (13%) of N-methylaniline and nitrous acid in addition to rearranged products. These side products could arise from reduction of both radicals as shown in Figure 5.

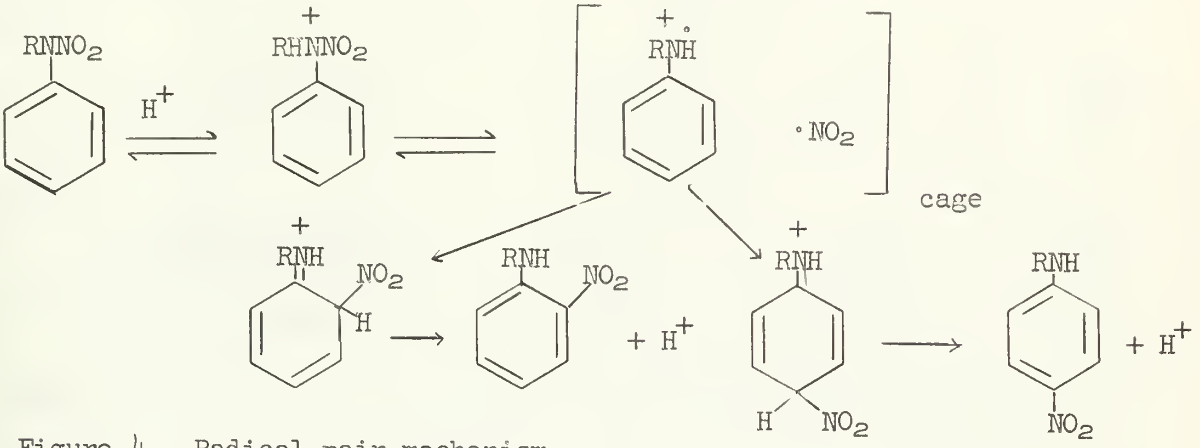


Figure 4. Radical pair mechanism.

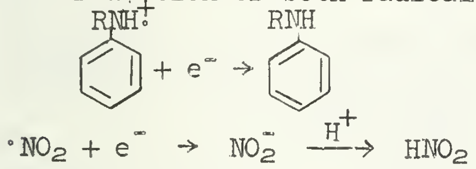


Figure 5. Reduction of intermediates in the radical pair mechanism.

PRODUCT STUDIES

The nitramine rearrangement has been studied in detail for four compounds under widely varying conditions. The ortho/para ratios and amounts of rearrangement products formed are listed in Table 2. No complete study of the side products of these reactions has been published but the available information is listed in Table 3. The formation of tars was reduced (with an accompanying increase in the recovery of rearranged products) by the addition of sodium azide to the reaction mixtures. This reagent apparently destroys any nitrous acid formed which would otherwise react with products to form tars. Banthorpe and Hughes have established[7] that added nitrous acid does not react with starting material but can react with the rearrangement products of I to form tars and reacts quantitatively with the products of III and IV to form tars.[9] Trace amounts of nitrobenzene and nitrophenols, which could arise from the diazotization of the products of I, have been detected. Formation of aryl amines seems to be restricted to the reaction of II under the conditions listed (Table 3) and no amines were detected in any other experiments.

The formation of nitrous acid can be explained by the π-complex theory and the cartwheel mechanism by a postulated formation of a dication as shown in Figure 6. This process could be assisted by protonation of the leaving NO_2^- group. The dication would then decompose to tars (or be reduced to the amine in the reaction of II) leaving nitrous acid to react with products. Nitrous acid would result from the reduction of nitrogen dioxide in the radical pair mechanism. Although there are no obvious reducing agents in the medium, White[4] suggests that easily oxidizable side products (which would decompose to tars) could act in this way.

The rearrangement products observed are not easily explained by the radical pair mechanism. The collapse of the radical pair to form products after multiple collisions would be expected to give a statistical distribution of products. The results are in qualitative agreement for the aniline derivatives but there is a large discrepancy for the naphthyl derivatives, III and IV (Table 2).

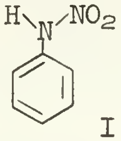
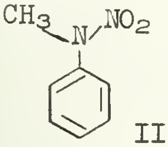
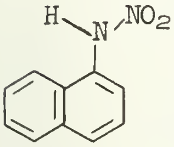
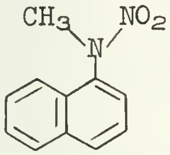
Compound	Conditions	2/4 ratio	2/4 ratio statistical	% Rearr.
 I	3 $\underline{M}$ $HClO_4$, 0°	2.34	2.0	60
	11.2 $\underline{M}$ $HClO_4$, 0°	10.1	2.0	95
 II	0.5 $\underline{N}$ HCl, 40°	1.68	2.0	83
 III	3 $\underline{M}$ $HClO_4$, 0° 60% dioxan-water	3.0	1.0	91
	15.6 $\underline{M}$ H_2SO_4, 0°	5.25	1.0	93
 IV	16 $\underline{M}$ H_2SO_4, 0°	> 10	1.0	86

Table 2. Rearrangement products.

Compound	Conditions	Side Products	Total %
I	> 10 $\underline{M}$ H_2SO_4, 0°	HONO + Tars	< 5
	3 $\underline{M}$ H_2SO_4, 0°	HONO	30
II	0.5 $\underline{N}$ HCl, 40°	N-methylaniline + HONO 10% 13%	< 13
IV	2.38 $\underline{M}$ H_2SO_4, 0°	< 1.0% HONO + Tars	20
	12.5 $\underline{M}$ H_2SO_4, 0°	10-15% HONO + Tars	--

Table 3. Side products.

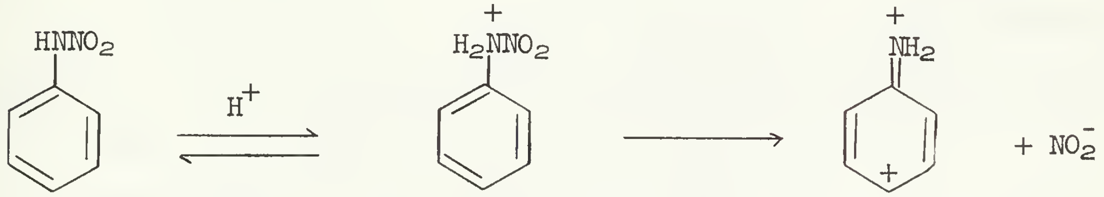


Figure 6. Ionization of N-nitro-arylamines.

Attempts to observe any intermediates which would distinguish between possible mechanisms have been unsuccessful. The addition of radical scavengers which do not react with nitrous acid has failed to give indication that radicals are involved in the process. In addition, no e.s.r. signal is observable which can be attributed to any radical intermediate. Likewise, no positive evidence for the existence of C-nitrites could be obtained and attempts to synthesize these compounds met with failure.

KINETIC STUDIES

The kinetics of the nitramine rearrangement have been studied in detail for four compounds[5-9,11] as shown in Table 4. In each case the rate of product formation was first order in substrate. A plot of log k_1 against $-H_o$ was linear with a slope greater than one and approximately a three-fold increase in the rate was observed when the reactions were carried out in deuterated solvent. These results rule out most chain processes and mechanisms where one substrate molecule nitrates another[17] and they indicate that the initial step is a pre-equilibrium protonation of the substrate.[7,9,11] The steep Hammett plots are suggestive of an A1-type decomposition of the protonated intermediate[18] as are the large solvent isotope effects.[19,20] Banthorpe and Hughes point out, however, that steep Hammett plots can arise from ionic strength effects alone at high acidities[21] and the solvent isotope effects probably give the most reliable data. These results are consistent with all three mechanisms under consideration but have been used to rule out many other possible reaction pathways.

Compound	Medium	Temperature	Slope of log k_1 vs. $-H_o$	k_{D_2O}/k_{H_2O}
I	1.7 M-3.6 M $HClO_4$	25°	1.35 ± 0.05	3.3
II	0.1 N HCl	40°	1.19	~3
III	1 M-2.25 M $HClO_4$ 60% dioxan-water	0°	1.37 ± 0.10	3.1*
IV	1.85 M-3.25 M $HClO_4$ 60% dioxan-water	0°	1.30 ± 0.10	2.5*

Table 4. Kinetic studies.

*Values corrected because solvent was not completely deuterated.

Ortho and para deuteration of these compounds gave no observable alteration of the rate of rearrangement. The proportions of ortho and para products were altered in the case of N-nitroaniline, I, however, and N-nitro-1-naphthylamine, III, gave a significant change in the total proportion of reaction leading to rearrangement (Table 5). The rate of protium-deuterium exchange in the substrate was found to be

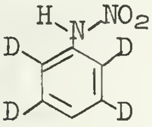
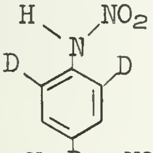
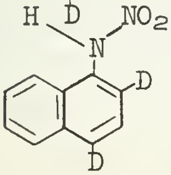
Compound	Conditions	% 2-Isomer*		% Rearrangement	
		Normal	Deuterated	Normal	Deuterated
	75% aq. H_2SO_4 -20°	95	95	--	--
	37% aq. $HClO_4$ 0°	72	68	--	--
	50% aq. $HClO_4$ 0°	75	82	--	--
	26% aq. $HClO_4$ 0°	70	83	--	--
	3.0 M $HClO_4$ 60% dioxan-water 0°	75	77	91	69
	15.6 M aq. H_2SO_4 0°	84	87	93	61

Table 5. Products of normal and deuterated N-nitro arylamines. *Remainder is 4-isomer.

insignificant compared to the rate of rearrangement in these experiments.[7,9] N-methyl-N-nitroaniline[11] gave no product isotope effect under the conditions employed but the rate of protium exchange was not reported in this case.[11] No results for deuterated N-methyl-N-nitro-1-naphthylamine have been reported although its synthesis from the precursor to 2,4-dideutero-N-nitro-1-naphthylamine would not be expected to be difficult.

In the case of the aniline derivative, 2,3,5,6-tetra- and 2,4,6-tri-deuterated substrates were employed for experimental convenience. The results indicate (a) that ortho-deuteration leads to more para product but that para-deuteration more than undoes this effect and (b) that the product isotope effect is most important at low acidities. Calculated[7] values for the ortho and para product kinetic isotope effects are 1.2 and 2.5, respectively, at low acidities. These effects are probably too large to be attributable to secondary isotope effects. The results for the naphthyl derivative are in agreement with the aniline case although the effect is small.[9] Thus, since the overall rate of reaction is not altered by deuteration, it is likely that the rate expression for product formation is a function of rate constants referring to steps in which C-H bonds are broken but that these steps occur after the overall rate determining step. For the naphthyl case, presumably an intermediate on the reaction pathway is partitioned between rearrangement and disproportionation and no isotope effect occurs in the branch leading to side products.

These results are easily accounted for by the cartwheel mechanism. A rate determining step prior to the rearrangement of C-nitrite intermediates to products should give no overall rate change on deuteration but would be expected to give more para isomer on ortho deuteration. C-nitrites could be partitioned between rearrangement and disproportionation products, thus accounting for the results in the naphthyl case.

These results are difficult to explain using π-complex or the radical pair mechanism. Both pathways pass through Wheland intermediates before C-H bond breaking is completed. Since no deuterium isotope effect is observed in nitrations with NO_2^+ (which pass through identical Wheland intermediates), by analogy none would be expected in this case. Also, the radical pair mechanism would require a reversible condensation of the radical pair to form the Wheland intermediates in order to explain the large effect of para deuteration of the ortho/para product ratio.

The failure to observe any product kinetic isotope effect in N-methyl-N-nitroaniline is likewise difficult to explain by the cartwheel mechanism. Banthorpe and Hughes[17] have observed, however, that the conditions of this experiment, namely "low acid concentration" (0.5 N hydrochloric acid) and "high temperature" (40°), seem ideal for the appearance of a thermal rearrangement as a component of the reaction such as that found for N-methyl-N-nitro-1-naphthylamine.[22] This possibility was not checked.[11] As was pointed out earlier, the rate of deuterium-protium exchange was not reported in this experiment. It is possible that no isotope effect was observed simply because "all" of the label was washed out of the molecule before appreciable rearrangement could take place.

A final piece of kinetic data has been reported.[11] The rearrangement of a series of para-substituted N-methyl-N-nitroanilines was found to obey a linear Hammett σ^+-ρ relation (ρ = -3.9). The para substituents were not listed in these experiments and no data was reported which showed that nitroanilines were the products. In the presence of other substituents, reactions may have taken place which might have been quite different from the rearrangement under consideration. These data can be explained by each of the three mechanisms, however, in that each process allows for the introduction of positive charge into the ring in such a manner that a para substituent could take part in the resonance interaction.

Proponents of the cartwheel mechanism have found no evidence that the rearrangement from N-nitro- to N-nitrite- intermediates is required as their original mechanism predicts. They have accordingly removed this step from their mechanism and postulate a direct N-nitro to C-nitrite shift prior to formation of products (Figure 7).[9]

SUMMARY

Of the three mechanisms considered, the cartwheel mechanism explains the greatest

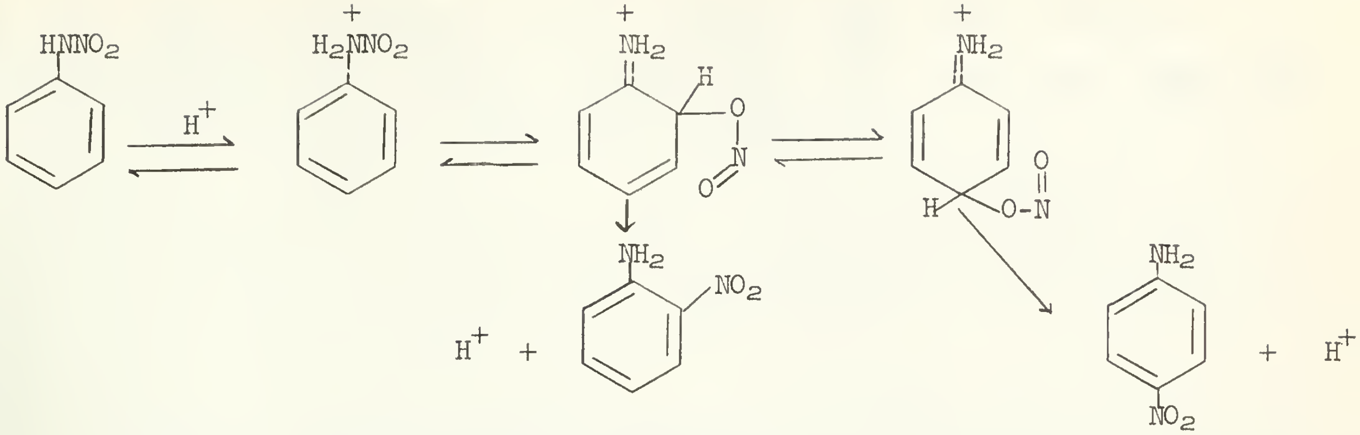


Figure 7. Modified cartwheel mechanism.

body of data. The only area which is not in agreement with this mechanism is the failure to observe a product kinetic isotope effect in 2,6-dideutero-N-methyl-N-nitroaniline. None of the mechanisms advanced to date adequately explain the apparent effect of N-methylation on isotope effects, however, although the kinetics and products of N-methyl rearrangements are similar to their primary analogs.

As they have been formulated, the π-complex and the radical pair mechanism cannot explain the observed product kinetic isotope effects. There seems to be no way that the radical pair mechanism could be modified to account for these data; but the π-complex mechanism might be modified such that Wheland intermediates are avoided. As in the cartwheel mechanism, direct electrophilic ejection of hydrogen might be postulated. Such an hypothesis would place this mechanism on no more shaky ground than the cartwheel mechanism.

It is apparent that more work must be done in this field before a mechanism can be firmly established. The effects of the N-methyl group of the reaction remains a mystery as does the exact mechanism of aromatic hydrogen loss. It should be established what the reason is for the failure to observe a product kinetic isotope effect in the rearrangement of II. An experiment should be run with 2,4-dideutero-N-methyl-N-nitro-1-naphthylamine, also, to test whether an isotope effect can be observed in this case.

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OXIDATIVE CYCLIZATIONS OF ALCOHOLS WITH LEAD TETRAACETATE

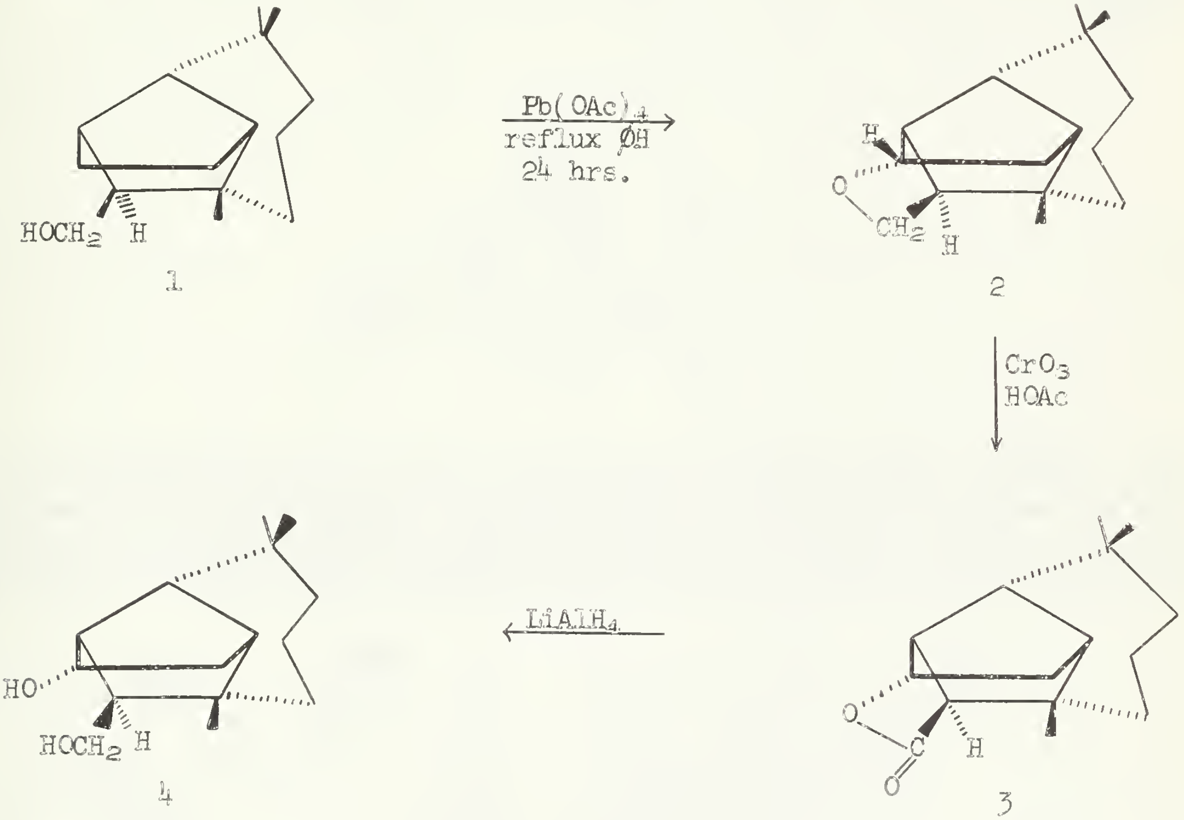
Reported by Donald C. Schlegel November 6, 1967

INTRODUCTION

In the late 1950's a new application of the already important reagent, lead tetraacetate, was discovered.[1] Certain steroid alcohols when treated with lead tetraacetate in non-polar media formed five-membered cyclic ethers in high yield.[2] More recently this reaction has been extended to primary and secondary aliphatic alcohols, unsaturated alcohols and large ring alcohols with interesting results. This seminar will deal largely with these latest extensions of the reaction and the mechanistic attempts to explain these results.

CYCLIZATION IN FIXED GEOMETRIC SYSTEMS

Lead tetraacetate has long been known as an efficient reagent for the oxidation of primary alcohols to aldehydes and secondary alcohols to ketones in polar media.[3] Only recently, however, was it discovered that in non-polar media such as benzene or cyclohexane could cyclic ether formation be brought about. This new reaction was first discovered in the steroid field.[1] Here it gave an easy synthetic procedure for activating a normally unreactive position. A recent example of this activation in another field, the terpenoid series, involved the oxidation of isolongifolol[4] (1) with lead tetraacetate in refluxing benzene to give isolongifolanoxide (2).



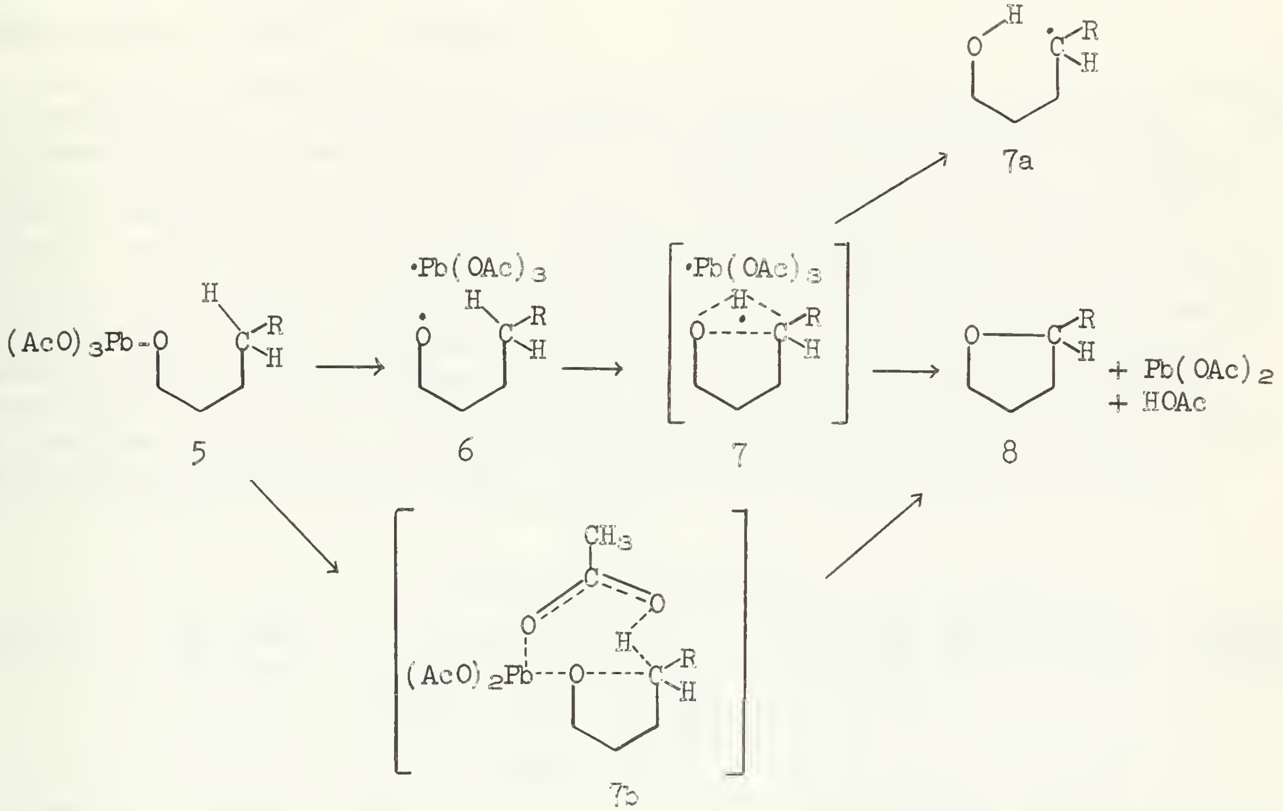
Oxidation of this oxide with chromium trioxide in acetic acid and cleavage of the resulting lactone (3) with lithium aluminium hydride yielded isolongifolane diol (4), a material now obtaining a functional group at a normally unreactive position.

Experimentation with may different sterols showed that a critical distance exists in these fixed ring systems between the reacting oxygen and carbon atom.[2] If this distance is between 2.5-2.7A°, an intramolecular ether linkage is formed. If the distance exceeds exceeds 2.8A°, intermolecular and fragmentation reactions occur with the exclusion of intramolecular ether formation.

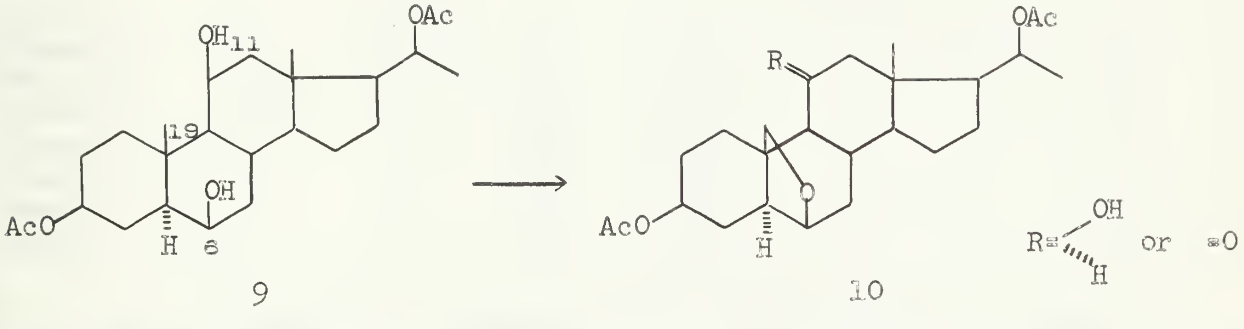
In fixed ring systems a free radical mechanism has been proposed.[2] The initial step involves the formation of a lead alkoxide.

$$ROH + Pb(OAc)_4 \rightleftharpoons RO\text{-}Pb(OAc)_3 + HOAc$$

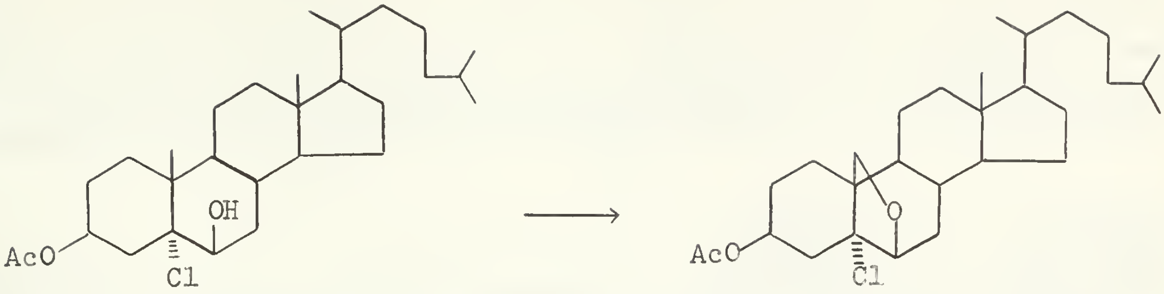
Experimentation has shown that lead tetraacetate does not decompose in the absence of a catalyst[5,6] below 140°.[7] However, homolytic cleavage of the alkoxide bond is readily brought about in either refluxing benzene or cyclohexane or photolytically at low temperature.[2,8,9] It has been suggested that radical intermediate (6) then passes through the transition state symbolized by (7) to form cyclic ether (8). A variation of the postulated mechanism might involve the direct conversion of intermediate (5) through a transition state (7b) to the cyclic ether (8).



An intermediate such as (7a) is considered unlikely because treatment of 6β, 11β-hydroxysteroid (9) in which lead tetraacetate predominantly attacks the 6β-hydroxyl due to steric reasons, yielded only one cyclic ether, the 6β, 19-ether (10) even though the C-19 carbon is equally distant from both the C-6 and C-11 hydroxyl groups.[2]



Evidence for operation of the same cyclization mechanism under both thermal and photolytic reaction conditions came when Kalvoda and Heusler[9] treated 3β-acetoxy-5α-chloro-6β-hydroxycholestane with lead tetraacetate in benzene either photolytically at 16-18° or thermally under reflux and found comparable product yields and composition. The major product was again the 5-membered cyclic ether. Consequently, they concluded that the proposed radical mechanism for cyclization was operable under either photolytic or thermal conditions.



CYCLIZATION OF ALIPHATIC ALCOHOLS

Late in 1963 Mihailovic[10] published the first in a series of papers investigating the action of lead tetraacetate on saturated primary and secondary alcohols. He and his coworkers found that on treatment of an aliphatic alcohol such as 5-nonanol in a 1:1 mole ratio with lead tetraacetate in refluxing benzene, the lead tetraacetate was rapidly consumed and a cyclic ether could be isolated from the reaction mixture as the major product in 30-40% yield. The addition of larger amounts of lead tetraacetate, 1.5 to 2 moles per mole of alcohol, did not noticeably alter the production of cyclic ether, only lengthened the reaction time. The following table shows the major products of other alcohols submitted to 1:1 mole ratio, alcohol:lead tetraacetate, oxidation in refluxing benzene in the presence of calcium carbonate.[11] Other products obtained in small yield were formaldehyde (traces), formate ester of the starting alcohol (0.5-3%), acid derived from the starting alcohol (traces-1%), and the corresponding ester (1-3%), and some high boiling products containing acetate groups which were not investigated.

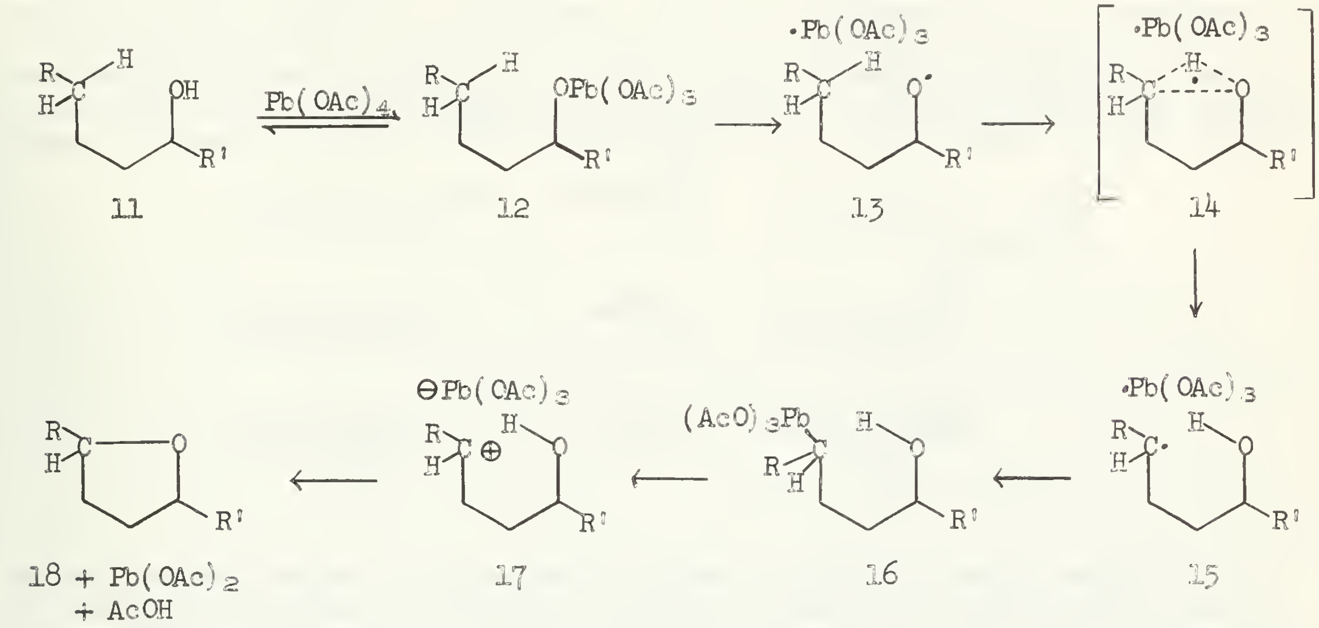
Table I
(Product Yields in %)

Alcohol	Rx. time[a] in hours	Tetrahydrofuran			Aldehyde + Acetal	THP[d]	Acetate	Unreacted Alcohol
		2-alkyl	2,5-dialkyl cis + trans	ratio cis/trans				
1-Butanol	12 1/2	20	--	--	0 + 5	0	15	16
1-Pentanol	2 1/4	43	--	--	3 + 1	0	9.5	10
1-Hexanol	1 1/4	49.5	--	--	2	3	9	9
1-Heptanol	3/4	49.5	--	--	2	3.5	9	10.5
1-Octanol	1 1/2	48	--	--	1.5	4	9	10
1-Dodecanol	2 1/4	49	--	--	2	3	b	b
					Ketone			
2-Pentanol	26	9.5	--	--	b	0	b	c
2-Hexanol	4	--	41	40:60	3.5	0	12	c
3-Heptanol	8 1/2	--	41	40:60	5	0	11	c
2-Octanol	2 1/2	--	40	40:60	3	1	9	c
4-Octanol	14	2	39	45:55	5	b	17	c
3-Nonanol	7	--	38	43:57	3.5	b	b	c
4-Nonanol	13	2	38	45:55	4.5	0	16	c
5-Nonanol	2	--	33	43:57	4	0	9	c

[a] In refluxing benzene until a negative starch-iodide test was obtained
[b] Not determined
[c] Varied between 10-20% for these alcohols
[d] Tetrahydropyran

The oxidative results of both primary and secondary alcohols show that the five-membered cyclic ether is formed in great preponderance over or in complete exclusion

of the six-membered cyclic ether. Tetrahydrofuran formation is thus the major product in both the fixed ring systems of sterols[2] and with aliphatic alcohols. Mihailovic accounts for this by assuming "that the conformation which can be adopted by the six-membered transition state (14) is more favorable than that of a seven-membered cyclic structure necessary for 1,6-transfer."[11] To explain the remainder of the data Mihailovic postulated a modified mechanism for lead tetraacetate cyclizations in the aliphatic alcohol series.



The results indicate that alcohols such as 1-butanol and 2-pentanol which have methyl hydrogens on the δ-carbon atom react much more slowly than the other primary and secondary alcohols having methylene hydrogens on the δ-carbon atom. Previous work[12] had shown that the order of ease of 1,5 hydrogen transfer to an alkoxy radical is secondary hydrogen > primary hydrogen, leading to the more stable secondary alkyl radical. Consequently, assuming similar circumstances in the case of lead tetraacetate cyclizations, the observed more rapid reactions of alcohols having secondary hydrogens on the δ-carbon atom over alcohols having only primary hydrogens on the δ-carbon atoms may be explained by the hydrogen transfer from intermediate (13) to form intermediate (15).

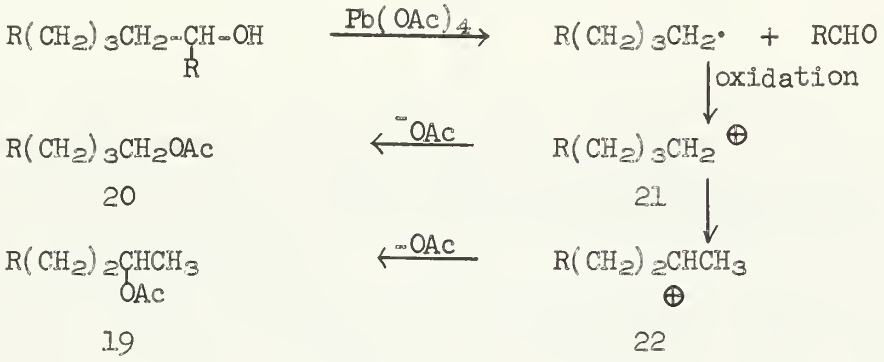
Mihailovic,[11] on comparing the reaction times of the alcohols in Table I, found several correlations. In the alcohol series where R = variable and R' = constant, the reaction times proceed as follows, for R' = H: 1-pentanol (R = CH_3) > 1-hexanol (R = C_2H_5) > 1-heptanol (R = n-C_3H_7) < 1-octanol (R = n-C_4H_9) < 1-dodecanol (R = n-C_8H_{17}); similar results for R' = CH_3, C_2H_5 and n-C_3H_7. From these correlations he concluded that stabilization of the alkyl radical and carbonium ion of intermediates (15) and (17) increases with the length of the R group through R = n-C_3H_7. For R groups larger than R = n-C_3H_7, however, the reaction time again increases due to steric hindrance of the abstractable δ-hydrogens by the R, alkyl group in the coiled conformation.

While the positive inductive effect of the various R groups has the capability of stabilizing a carbonium ion or an alkyl radical, this effect cannot influence the rate of the reaction at both intermediates. Mihailovic has not indicated what is the slow step (rate determining step) of his proposed mechanism. Whether the positive inductive effect of the R group influences a slow step leading to intermediate (15) or (17) or indeed whether it aids in the removal of the δ hydrogen from intermediate (13) is still in doubt.

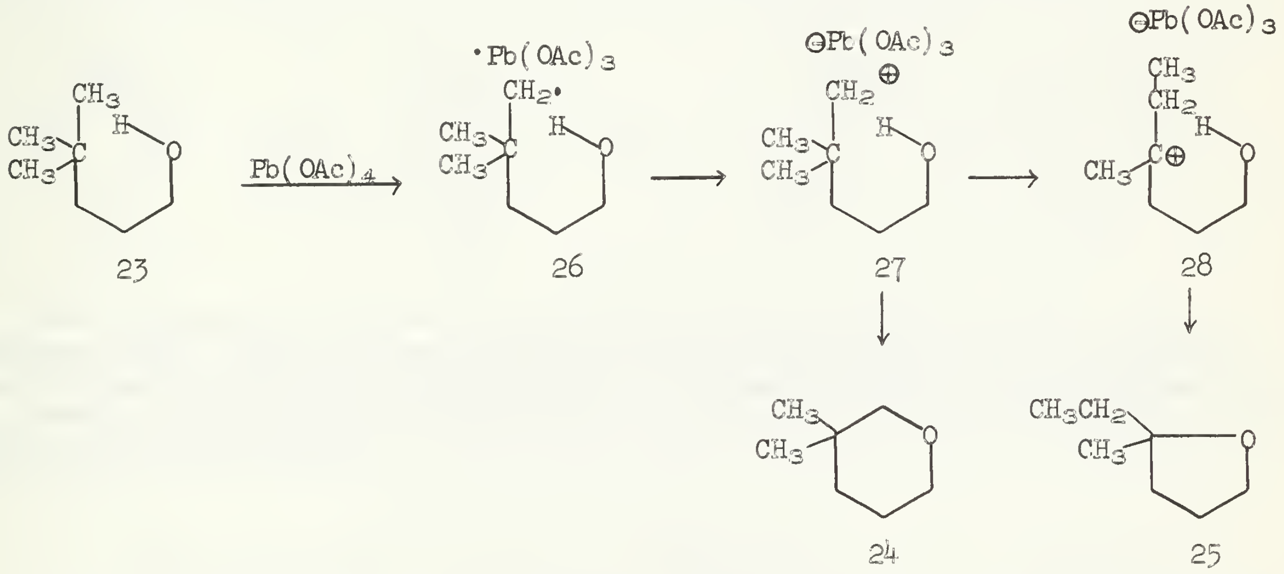
In a second comparison in which R = constant and R' = variable Mihailovic found that the reaction time varies as follows, for R = H: 1-butanol (R' = H) < 2-pentanol (R' = CH_3); for R = CH_3: 1-pentanol (R' = H) < 2- hexanol (R' = CH_3) < 3-heptanol (R' = C_2H_5) < 4-octanol (R' = n-C_3H_7) > 5-nonanol (R' = n-C_4H_9). The series shows

that increasing the length of R' group attached to the carbinol carbon increases the reaction time. Apparently, the positive inductive effect of the increasing series of R' groups increases the electron density of the alkoxy radical and thereby decreases its electrophilic properties as a hydrogen abstracting agent.

Studies of the minor fragmentation products of the reaction have led Mihailovic[11,13] to postulate the further oxidation of the alkyl radical to the corresponding alkyl carbonium ion. The finding of the 2-(19) as well as the 1-alkyl acetate (20) brought about this conclusion. Earlier work had shown that radicals do not undergo a 1,2 hydrogen shift,[14,15] consequently, he postulated the intermediacy of carbonium ion (21) which can then undergo a 1,2 hydride shift to the more stable secondary carbonium ion (22). In the secondary alcohols studied the combination of the 1- and 2-alkyl acetates was 1 to 1.6% with the 2-alkyl acetates formed in greater yield.[11] Mihailovic suggests that this oxidation of an alkyl radical may be similar to oxidations of carbon radicals by cupric salts.[16]



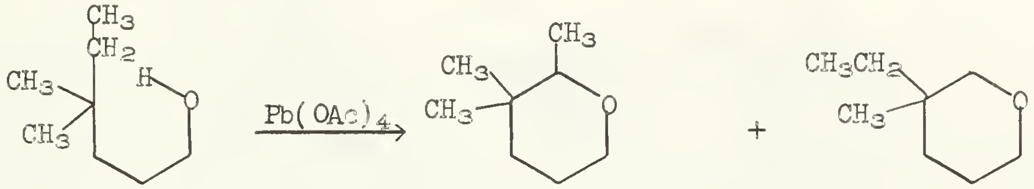
As further evidence for the intermediacy of carbonium ion species in lead tetraacetate oxidations of aliphatic alcohols, Mihailovic[17] presents the case of 4,4-dimethyl-1-pentanol (23). This alcohol contains no δ-hydrogens and therefore the only expected ether product would be 3,3-dimethyltetrahydropyran (24). This product was isolated in 4-6% yield but surprisingly 2-ethyl-2-methyltetrahydrofuran (25) was also found in 1% yield. Mihailovic explains the presence of this latter species by suggesting that the initially formed alkyl radical (26) was oxidized to the primary carbonium ion (27) which can then either react immediately to form the tetrahydropyran or rearrange to the more stable tertiary carbonium ion (28) by a 1,2 methyl shift. This species in turn would form the 5-membered ring.



Further investigation as to whether this 1% of rearranged product is real would be of value. The purity of the 4,4-dimethyl-1-pentanol was checked by glc but Mihailovic does not relate how many columns were utilized or whether an actual sample of 4-methyl-1-hexanol could be separated from 4,4-dimethyl-1-pentanol under

the glc conditions used. The absence of any rearranged tetrahydrofuran in the 4,4-dimethyl-1-hexanol case discussed below also casts some doubt that a carbonium ion initiated rearrangement does occur.

When 4,4-dimethyl-1-hexanol (29) was treated under similar oxidative conditions to 4,4-dimethyl-1-pentanol no tetrahydrofuran was isolated. Only two tetrahydropyrans, 2,3,3-trimethyltetrahydropyran (30), 8%, and 3-ethyl-3-methyltetrahydropyran (31), 3%, were found.

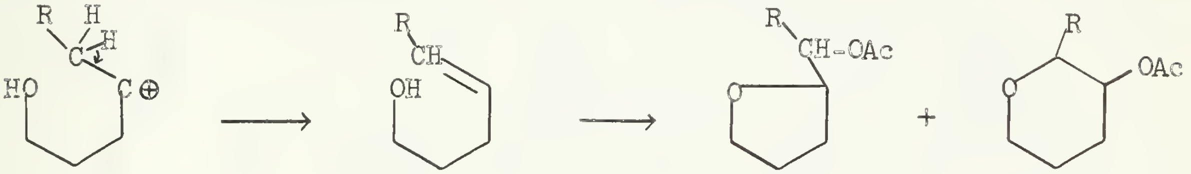


29 30 31

The yields again indicate the greater ease of abstraction of secondary over primary hydrogens but gives no further evidence in support of a carbonium ion intermediate. In another run of the above reaction in the presence of a catalytic amount of benzoyl peroxide the yield of the 2,3,3-trimethyltetrahydropyran was increased to 13% and that of 3-ethyl-3-methyltetrahydropyran to 4%. The reaction time also decreased from 12 down to 5 hours.

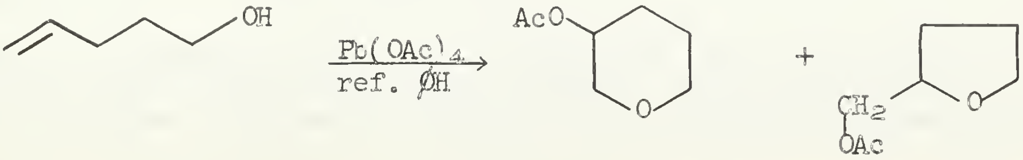
The influence of catalytic amounts of benzoyl peroxide on the reaction is difficult to explain with any of the proposed mechanisms. Further investigation of this point would be in order to recheck if the increase in the six membered cyclic ethers is real. The effect of benzoyl peroxide in lead tetraacetate oxidations where the five membered ether can be formed would also be of interest. If cyclic ether formation is truly increased and reaction time shortened in these cases, then a mechanism involving a radical chain will have to be postulated.

Some evidence, however, leaves the intermediacy of a carbonium ion in doubt. If a carbonium ion was an intermediate in the cyclization of aliphatic alcohols with lead tetraacetate one might expect to find one or both of the following ether acetates among the reaction products.[2,16] So far Mihailovic has not reported the isolation of such products.



32 33 34 35

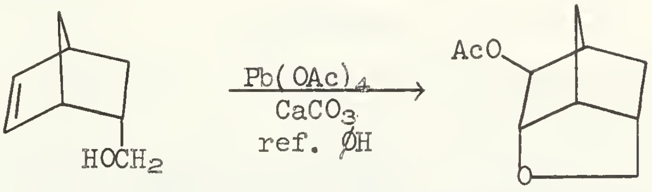
That unsaturated alcohols can react with lead tetraacetate to form ether acetates in fair yield has been shown by several workers.[18-20] Moon and Lodge[19] reacted 4-penten-1-ol in refluxing benzene with lead tetraacetate and obtained among the products 3-acetoxytetrahydropyran (37) in 26% yield and tetrahydrofurfuryl acetate (38) in 14% yield.



36 37 38

Under similar conditions 5-hexene-1-ol gave 2-acetoxymethyltetrahydropyran in 37% yield.[20]

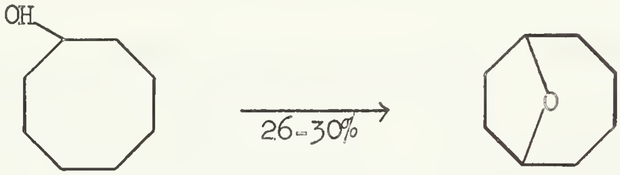
At the same time Moriarty and Kapadia,[18] while studying unsaturated bridged ring alcohols found that 2-α-hydroxymethylbicyclo[2,2,1]hept-5-ene (39) was converted by lead tetraacetate under conditions similar to those used by Mihailovic to 6-oxatricyclo[3,2,1,1]nonan-4β-ol-acetate (40).



39 40

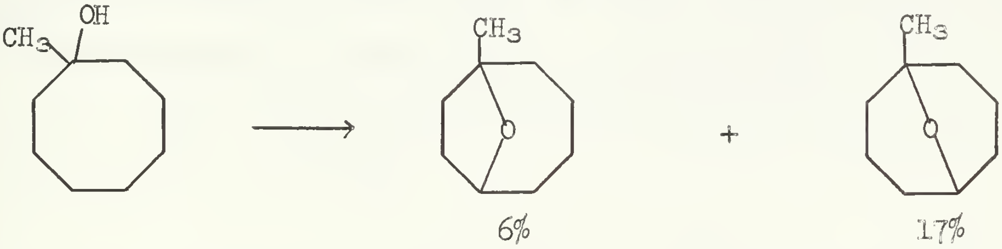
ACTION OF LEAD TETRAACETATE ON LARGE RING ALCOHOLS

Two sets of workers[21,22] have investigated the action of lead tetraacetate on cyclic alcohols. Both found that cyclooctanol (41) gave 1,4-epoxycyclooctane (42) as the exclusive oxide product although the proposed intermediate oxygen radical would be equally close to both the C-4 and C-5 hydrogens. Again the lower energy of the six-membered ring transition state is suggested to explain the results.



41 42

Cope and coworkers[21] found, however, that 1-methylcyclooctanol gave the 1,4- and 1,5-epoxy compounds in a 1:3 ratio. They suggested that the introduction of the methyl group must alter the geometry of the cyclooctane ring either in the ground or



transition state so as to favor 1,5 over 1,4 epoxide formation.

In other experiments Cope and coworkers[21] found that cycloheptanol gave a 5% yield of 1,4-epoxycycloheptane and on the basis of preliminary studies 1-methylcycloheptanol gave 1-methyl-1,4-epoxycycloheptane in 1.5% yield. Cyclohexanol gave no epoxy compounds under similar conditions.

CONCLUSION

Treatment of primary and secondary alcohols with lead tetraacetate in non-polar solvents yields cyclic ethers as the major product. In most cases the five membered cyclic ethers are formed in great preponderance over the equally probable six membered cyclic ethers. The greater stability of six over the seven-membered transition state is postulated as the explanation.

In the fixed ring alcohols such as sterols a totally radical mechanism is postulated in both the thermal and photolytic oxidations. With aliphatic primary and secondary alcohols, however, the intermediacy of a carbonium ion is also suggested. The inability to find α-acetoxy ethers among the oxidation products of aliphatic alcohols, though, puts the intermediacy of this carbonium ion in some doubt. More work is definitely needed to fully elucidate the mechanism of this reaction.

Cyclic alcohols have also been treated with lead tetraacetate to yield in most cases the 1,4-epoxy compounds.

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THE STRUCTURE OF tRNA'S

Reported by W. T. Shier November 9, 1967

INTRODUCTION

The relationship between DNA and protein synthesis can be summarized by the formula

$$\begin{tikzcd} \text{DNA} \arrow[r, "\text{transcription}"] \arrow[d, shift left] & \text{RNA} \arrow[r, "\text{translation}"] & \text{protein} \\ \text{DNA} \arrow[u, shift left] & & \end{tikzcd}$$

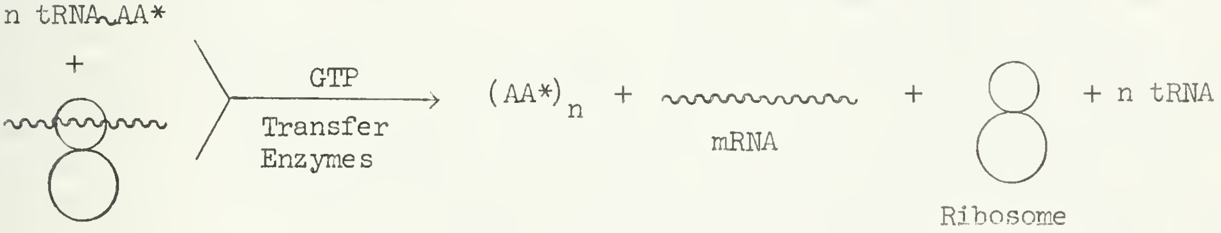
This relationship is known as the central dogma. In the mid-1950's, while the general validity of the central dogma was becoming obvious, it was also apparent that amino acids possess no specific affinity for RNA. Moreover, not all RNA molecules are templates; there exist at least two additional classes of RNA, each playing a vital role in protein synthesis. At this stage Crick[1] put forward the adaptor hypothesis: there is something that determines the sequence of the protein (mRNA) and the specificity is dependent on an adaptor (tRNA), and not the amino acid.

The adaptors were identified by Hoagland[2] as low molecular weight RNA molecules (tRNA) which carry labeled amino acids (AA*) from an activated complex to a peptide chain ($(AA^*)_n$) in a complex cell-free system consisting of the appropriate amino acyl tRNA synthetases (Enz), a message directing the incorporation of the labeled amino acids (mRNA), intact ribosomes, transfer enzymes, and the requisite energy sources (ATP,GTP). The mechanism is as follows:

$$\text{Enz} + \text{AA*} + \text{ATP} \rightleftarrows \text{Enz-AMP}{\sim}\text{AA*} + \text{PP}_i \qquad (1)$$

$$\text{PP}_i + \text{H}_2\text{O} \longrightarrow 2\text{P}_i \qquad (2)$$

$$\text{Enz-AMP}{\sim}\text{AA*} + \text{tRNA} \longrightarrow \text{tRNA}{\sim}\text{AA*} + \text{AMP} + \text{Enz} \qquad (3)$$



(4)

Hence, the crucial selection of an amino acid is done by an enzyme, an amino acyl tRNA synthetase, of high specificity. The validity of the adaptor hypothesis was established by a series of experiments carried out by Benzer[3] and his collaborators using a chemically induced mistake:

Abbreviations used in the text: A, adenosine; A*, unidentified nucleoside in serine tRNA, probably N^6-isopentenyladenosine; AA, amino acid; ala, alanine; ATP, adenosine-5'-triphosphate; C, cytidine; cys, cysteine; DEAE-, diethylaminoethyl-; DiHU, dihydrouridine; DiMeA, N^6,N^6-dimethyladenosine; DiMeG, N^2,N^2-dimethylguanosine; DNA, deoxyribonucleic acid; G, guanosine; GTP, guanosine-5'-triphosphate; I, inosine; MeC, 2-methylcytidine; 5MeC, 5-methylcytidine; MeI, 1-methylinosine; mRNA, messenger RNA; 2'OMe, 2'-O-methyl; ORD, optical rotatory dispersion; P_i, inorganic phosphate; PP_i, inorganic pyrophosphate; - or p, phosphodiester moiety; -Ⓟ or P, phosphomonoester moiety; pan RNase, pancreatic RNase; PNP, polynucleotide phosphorylase; RNA, ribonucleic acid; RNase, ribonuclease; T, ribothymidine; tRNA, transfer RNA; tRNA_{cys}, cys specific tRNA; U, uridine; U*, a mixture of U and DiHU; Y, unidentified component of yeast phenylalanine tRNA; ψ, pseudouridine.

$$\text{tRNA}_{cys}\sim\text{cys}^*\text{-SH} \xrightarrow{\text{Raney Nickel}} \text{tRNA}_{cys}\sim\text{ala}^*$$

$$\text{tRNA}_{cys}\sim\text{ala}^* \xrightarrow[\text{Protein Synthesis System}]{\text{cys directing mRNA}} \text{Protein}^*$$

$$\text{tRNA}_{cys}\sim\text{ala}^* \xrightarrow[\text{Protein Synthesis System}]{\text{ala directing mRNA}} \text{No Incorporation}$$

Thus, when a protein synthesizing system is presented with a hybrid adaptor-amino acid complex, it recognizes the adaptor and not the amino acid, as predicted by Crick.

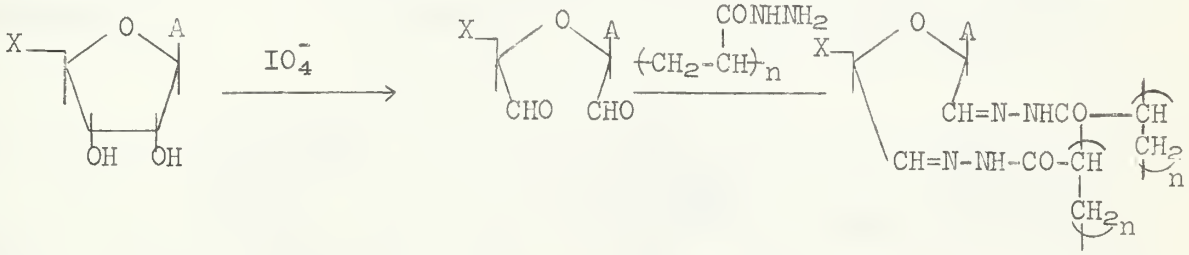
The adaptor hypothesis implies the existence of at least twenty distinct, specific tRNA's—one for each amino acid. Since the pioneering elucidation of the nucleotide sequence of yeast alanine specific tRNA, reported by Holley and collaborators in 1965,[4] the structures of four additional yeast tRNA's have been reported: two closely related serine tRNA's,[5] tyrosine tRNA,[6-8] and phenylalanine tRNA.[9] The structural work on all of the latter four tRNA's has followed the general principles and procedures developed by Holley in the elucidation of the primary structure of alanine tRNA; these principles and procedures form the basis of this seminar.

ISOLATION OF tRNA

Bulk tRNA is generally obtained by extracting intact cells with 90% phenol followed by removal of any contaminating polysaccharides, proteins, small oligonucleotides and ribosomal RNA by chromatography on DEAE-cellulose. Alternately, it may be isolated by adsorbtion from disrupted cell supernatants onto charcoal or ion exchange resins followed by elution with a salt gradient.[10]

FRACTIONATION OF BULK tRNA

To achieve a satisfactory purification of a given tRNA, the most difficult step in the structure elucidation, both physical and chemical methods have been employed. The most successful applications of ion exchange chromatography have used salt gradient elution from methylated serum albumin-kieselguhr (MAK) columns.[11] A very successful application of reversed phase partition chromatography using tricaprylylmethylammonium chloride in a Freon diluent adsorbed a diatomaceous earth support and elution by a concave sodium chloride gradient has recently been reported.[12] Holley and his associates have extensively exploited repeated counter current distribution in a potassium phosphate buffer-formamide-isopropanol solvent system.[13] Von Portatius, et. al.,[14] obtained a tenfold enrichment of valine tRNA by capitalizing on the conclusion of Preiss and collaborators[15] that the amino acid in charged tRNA is esterified to the 2'(3')-hydroxyl of a 3'-terminal ribose moiety. Bulk tRNA, previously freed of bound amino acids, was charged with valine, the 2',3'-diol system of the 3'-terminal ribose moieties of the uncharged tRNA's oxidized with periodate and these precipitated with polyacrylic acid hydrazide followed by 1-butanal:



The procedure is limited by the inaccessibility of completely amino acid-free tRNA.

The purification process can be monitored by charging the purification fractions with the appropriate C^{14}-labeled amino acid under the catalysis of a crude yeast

supernatant liquid after centrifugation at 100,000 x g (i.e., subjecting the tRNA to be assayed to reactions (1) to (3)), followed by acid precipitation of the charged tRNA and determination of the radioactivity incorporated into the precipitate. Alternately, bulk tRNA may be charged before fractionation using the appropriate C^{14}-labeled amino acid. The purification process may then be monitored by determining the radioactivity in each fraction.

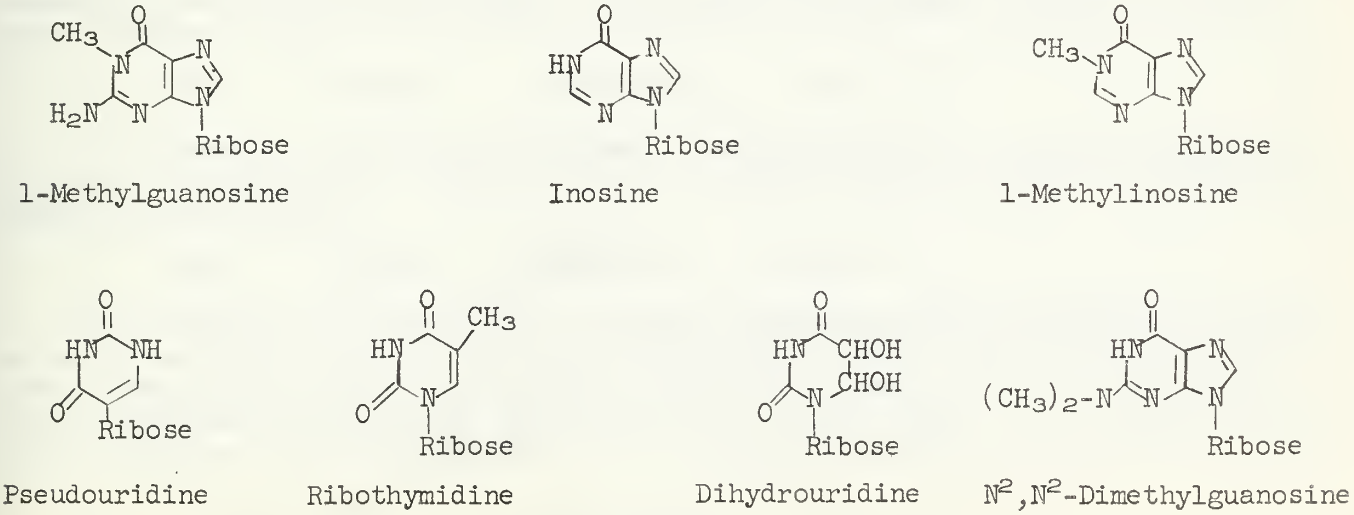
BASE COMPOSITION AND MINOR NUCLEOTIDES

tRNA's contain an unusually large number of "rare" or "minor" nucleotides in addition to the four major nucleotides. The determination of the structures of all of the component nucleotides in a given tRNA has represented a major hurdle in the complete structure determination; in a sense, the structure of phenylalanine tRNA is incomplete as reported,[9] since the structure of one minor nucleotide was unknown. Since Davis and Allen[16] in 1957 discovered the fifth nucleotide, later identified by Cohn[17] as pseudouridine, the structures of some twenty-three minor nucleotides, most of them methylated major nucleotides, have been reported.[18] Hall has outlined a general procedure for the isolation of minor nucleotides from yeast tRNA.[19]

Table I. Minor Nucleosides Isolated from Yeast tRNA[19]

Nucleoside	Mole Per Cent
N^6-Methyladenosine	0.39
2'(3')-O-Ribosyladenosine	0.013
N^6-(Aminoacyl)adenosines	0.034
1-Methylguanosine	0.090
N^2,N^2-Dimethylguanosine	0.236
N^2-Methylguanosine	0.014
3-Methylcytidine	0.018
5-Methylcytidine	0.084
3-Methyluridine	0.01
Ribothymidine	0.69
Pseudouridine	4.5
Inosine	0.22
1-Methylinosine	0.04
2'-O-Methyladenosine	0.028
2'-O-methyluridine	0.029
2'-O-methylguanosine	0.31
2'-O-methylcytidine	0.11
2'-O-methylpseudouridine	0.0009

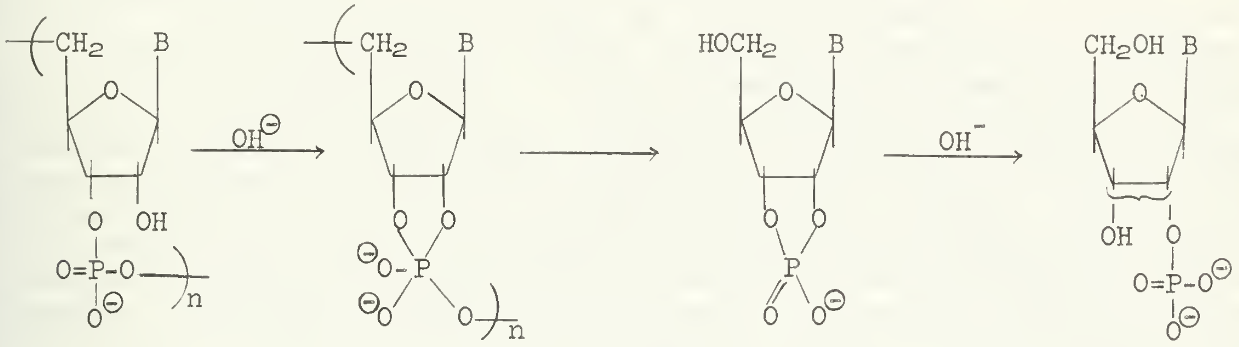
Figure 1. Structures of the minor nucleotides of yeast ala-tRNA



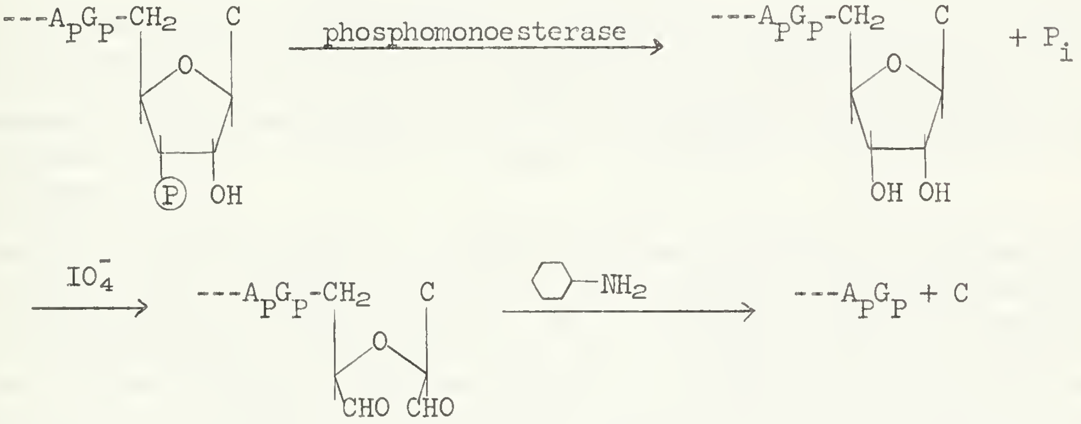
RNA DEGRADATIVE TECHNIQUES

In structural studies carried out to date, some use has been made of chemical degradative procedures in specific cases but the bulk of the studies have relied heavily on the use of hydrolytic enzymes of known specificities. The major degradative tools and their specificities are outlined below:

(1) Alkaline hydrolysis under Schmidt-Thannhauser conditions:[20] One normal sodium hydroxide at 37°C for 15 hr effects total hydrolysis to 2'(3')-ribonucleotides. Cleavage occurs distal to the 3'-phosphate due to intermediate formation of cyclic phosphate esters. In addition, complete hydrolysis is frequently achieved under milder conditions by the use of snake venom phosphodiesterase.[7]



(2) Stepwise chemical degradation: Neu and Heppel[21] have developed a procedure, subsequently refined by Weith and Gilman,[22] for the sequential removal of bases from the 3'-terminus of a polyribonucleotide chain. The terminal base released can be recovered and identified, and the cycle repeated, as illustrated below:



(3) Pancreatic RNase:[23] This enzyme catalyzes the hydrolysis of phosphodiester linkages distal to the 3'-phosphate of pyrimidine nucleotides (cytidine, uridine, pseudouridine, etc.).

e.g. $A_pC_pC_p \xrightarrow{\text{Pan RNase}} A_pC_p + C_p$

(4) RNase T_1: This enzyme, isolated from Taka-diastase by Egami and Sato,[24] catalyzes the hydrolysis of phosphodiester linkages distal to the 3'-phosphate of guanylic acid residues.

e.g. $A_pG_pC_p \xrightarrow{\text{RNase } T_1} A_pG_p + C_p$

(5) Micrococcal nuclease:[25] On large oligonucleotides this enzyme functions as an endonuclease, rapidly cleaving phosphodiester bonds to yield 3'-phosphoesters; when it is presented with small oligonucleotides it functions as an exonuclease, slowly removing 3'-nucleotides from the 3'-end of the chain. It is especially useful for elucidating the nucleotide sequence of tetranucleotides:

e.g. $^{5'}\ X_p(Y_p,Z_p)G_p{}^{3'} \xrightarrow[\text{nuclease}]{\text{micrococcal}} X_pY_p + Z_p + G_p$

(6) Alkaline phosphatase: The enzyme from E. coli[26] specifically catalyzes the hydrolysis of phosphomonoesters, but not phosphodiesters, while other structural features of the substrate play a relatively minor role.

(7) Polynucleotide phosphorylase:[7] Incubation of oligonucleotides with alkaline phosphatase followed by polynucleotide phosphorylase plus phosphate yields the 5'-hydroxyl terminal trinucleosidediphosphate.

FRACTIONATION OF OLIGONUCLEOTIDES

The complex mixtures of oligonucleotides resulting from enzymatic or partial alkaline hydrolysis offer a difficult separation problem. Gram quantities of hydrolysates are most conveniently separated by chromatography on columns of DEAE-cellulose, a procedure first introduced by Khorana and associates.[27] The discovery that 7M urea minimized adsorptive effects has greatly simplified this fractionation procedure.[28] The fractionation of milligram quantities of digests can be elegantly effected by two-dimensional paper or "mapping" techniques. Rushizky and Knight[29] introduced a method utilizing paper ionophoresis in the first dimension and paper chromatography in the second. The chromatograms were visualized under ultraviolet light or by the printing technique of Smith and Allen.[30] Sanger, et.al.,[31] obtained better resolution using two-dimensional high voltage paper ionophoresis at pH 3.5 on cellulose acetate in the first dimension and pH 1.9 on DEAE-paper in the second dimension. The enhanced resolution is achieved in the second dimension; the fractionation is due to both ion exchange and ionophoretic effects. A rapid electro-endosmotic flow of buffer carries the nucleotides through the paper subjecting them to ion exchange chromatography; superimposed on this and acting in the opposite direction to the ion exchange effect is an ionophoretic fractionation.

THE STRUCTURAL DETERMINATION OF OLIGONUCLEOTIDES

All of the structural studies reported to date have followed the general principles developed by Holley and his collaborators to elucidate the structure of alanine tRNA.[32] That is, the sequence determination of a purified tRNA assumes two phases: (1) the characterization of the total products obtained from complete degradation by the two RNases, pancreatic RNase and RNase T_1, and (2) the isolation and sequential analysis of large fragments obtained by partial enzymatic degradation until overlaps define a unique sequence.

Completion of the first phase is the most difficult.[6] The structures of mono- and dinucleotides can frequently be established from mobilities in the mapping procedures discussed above, followed by elution and ultraviolet spectrophotometric analysis (320 to 220 mμ) at pH 2, pH 7 and pH 13. Larger oligonucleotides are analyzed by determination of the molar ratio of nucleotides from the ultraviolet spectrum and further degradation by one or more of the procedures described above. Representative examples follow: (1) Sequence determination of $T_p\psi_p C_p C_p$—a sequence believed common to all tRNA's:[25] bulk tRNA $\xrightarrow{\text{RNase } T_1}$ $(T_p,\psi_p,C_p)G_p$. From the known specificity of RNase T_1, the nucleotide at the 3' terminus is G_p. bulk tRNA $\xrightarrow{\text{Pan RNase}}$ G_pT_p. Since the G_pT linkage would be cleaved by RNase T_1, T_p is placed at the 5' terminal, i.e., the partial structure is $T_p(\psi_p,C_p)G_p$. $T_p(\psi_p,C_p)G_p$ $\xrightarrow[\text{nuclease}]{\text{micrococcal}}$ $T_p\psi_p + C_p + G_p$. The dinucleotide was isolated by electrophoresis and a bathochromic shift in the ultraviolet spectrum at alkaline pH established that it contained ψ. Hence, ψ_p is the second nucleotide from the 5'-end and the nucleotide sequence is $T_p\psi_p C_p G_p$. (2) Sequence determination of $G_pG_pG_pA_pG_pA_pC$:[7] tyr tRNA $\xrightarrow{\text{Pan RNase}}$ (4Gp,2Ap)Cp. The specificity of pan RNase establishes Cp as the nucleotide at the 3' terminus. (4Gp,2Ap)Cp $\xrightarrow{\text{RNase } T_1}$ 3Gp + ApGp + ApCp. The dinucleotides were identified by chromatographic mobility and spectral criteria. This establishes the partial structure (3Gp,ApGp)ApCp. (3Gp,ApGp)ApCp $\xrightarrow[\text{+ PNP + } P_i]{\text{alkaline phosphatase}}$ $G_pG_pGOH + C_{\cancel{pP}} + 2A_{PP}$+G.

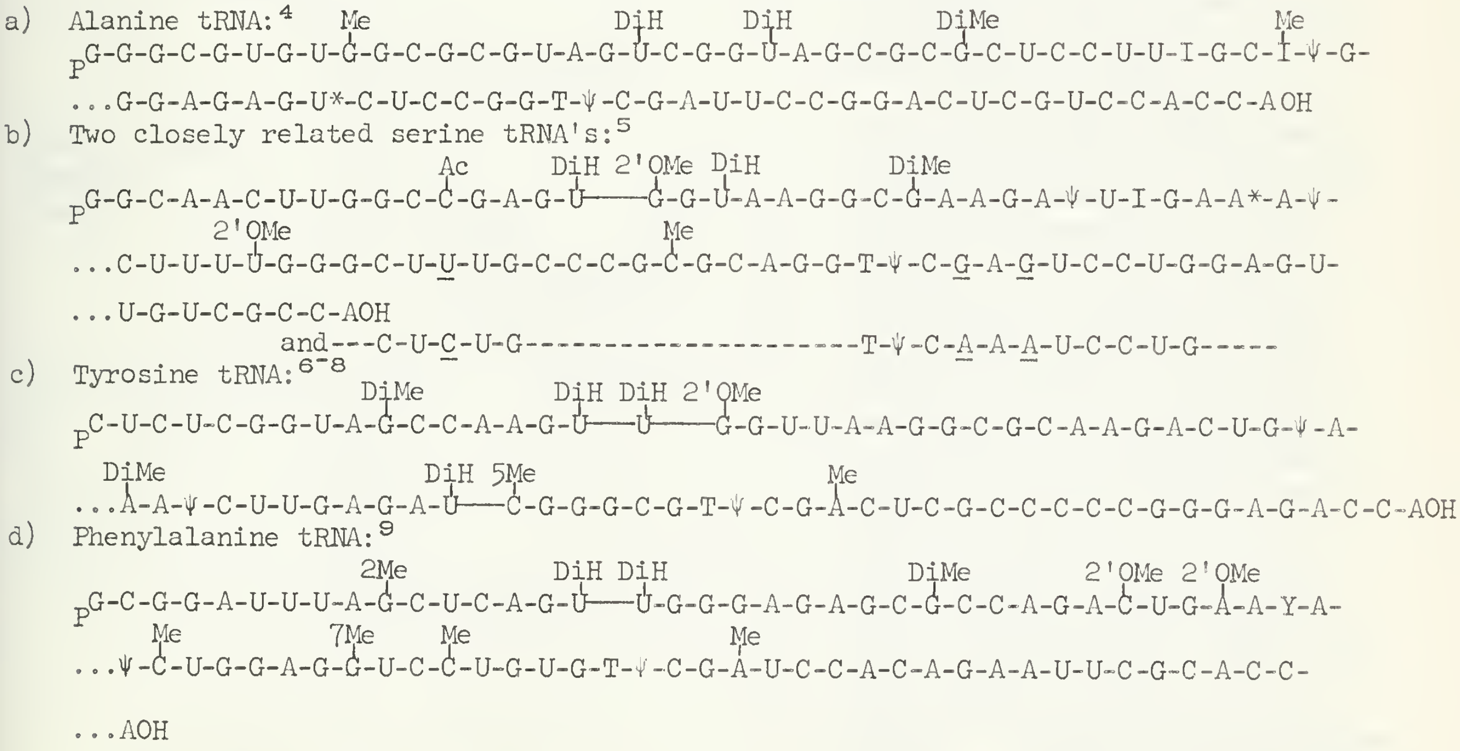
The trinucleosidediphosphate was identified by its spectral properties; the known specificity of PNP establishes that it constitutes the 5' terminus. The results are compatible only with the sequence $G_pG_pG_pA_pG_pA_pC_p$.

The second phase of the sequential analysis has been facilitated by the discovery that large oligonucleotides can be obtained by limited digestion using low concentrations of RNase T_1[33] or pan RNase[34] for short incubation periods at 0° in the presence of magnesium ions. After purification the large oligonucleotides are further degraded, ultimately to the small oligonucleotides obtained from complete enzymatic digestion. The nucleotide sequences of large oligonucleotides are determined until overlap of unique sequences permits the assignment of a single sequence. Minor nucleotides, especially if they occur only once in the tRNA molecule, greatly facilitate the establishment of unique overlaps.

THE PRIMARY STRUCTURE

The tRNA's possess a number of common features which tend to set them into a unique class of natural products. It had been hoped that when the primary structures of a few tRNA's would become known, the detailed mechanism by which they perform their adaptor function would become obvious- this has, in part, been realized. One approach to gathering clues to the nature of this mechanism has involved the search for features common to all tRNA's. Many of these common features were determined from studies on bulk tRNA, and others arose from a close analysis of the structures known to date.[9] It was early realized that all the tRNA's have a similar molecular weight corresponding to 70 to 80 nucleotides.[32,35] Ralph, et.al,[36] used their technique of labeling the 5'-phosphate groups with anilidate-C^{14} to show that most chains end in $_pG_p$. The amino acid acceptor end was established by periodate oxidation experiments to be the 3'-terminus with the amino acid esterified to the 2'(3')hydroxyl of the ribose moiety:[15] periodate oxidation of uncharged tRNA destroys the acceptor activity for all amino acids tested and similar treatment of tRNA charged with only one amino acid results in the loss of acceptor activity for all tRNA's except the one specific to the amino acid bound. Neu and Heppel[21] employed the stepwise chemical degradation procedure discussed above to demonstrate the presence of the sequence $-_pC_pC_pA$ at the acceptor end of all the tRNA molecules. Zamir, et.al.,[25] obtained the tetranucleotide $T_p\psi_pC_pG_p$ by RNase T_1 digestion of bulk tRNA and of three partially purified tRNA's in yields approaching one mole per mole of tRNA; they suggested that this sequence is common to all tRNA's.

Figure 2. The Known Primary Structures of tRNA's



a) Alanine tRNA:[4]

Me DiH DiH DiMe Me

$_p$G-G-G-C-G-U-G-U-G-G-C-G-C-G-U-A-G-U-C-G-G-U-A-G-C-G-C-G-C-U-C-C-U-U-I-G-C-I-Ψ-G-

...G-G-A-G-A-G-U*-C-U-C-C-G-G-T-Ψ-C-G-A-U-U-C-C-G-G-A-C-U-C-G-U-C-C-A-C-C-AOH

b) Two closely related serine tRNA's:[5]

Ac DiH 2'OMe DiH DiMe

$_p$G-G-C-A-A-C-U-U-G-G-C-C-G-A-G-U——G-G-U-A-A-G-G-C-G-A-A-G-A-Ψ-U-I-G-A-A*-A-Ψ-

2'OMe Me

...C-U-U-U-U-G-G-G-C-U-U-U-G-C-C-C-G-C-G-C-A-G-G-T-Ψ-C-G-A-G-U-C-C-U-G-G-A-G-U-

...U-G-U-C-G-C-C-AOH

and---C-U-C-U-G----------------------T-Ψ-C-A-A-A-U-C-C-U-G-----

c) Tyrosine tRNA:[6-8]

DiMe DiH DiH 2'OMe

$_p$C-U-C-U-C-G-G-U-A-G-C-C-A-A-G-U——U——G-G-U-U-A-A-G-G-C-G-C-A-A-G-A-C-U-G-Ψ-A-

DiMe DiH 5Me Me

...A-A-Ψ-C-U-U-G-A-G-A-U——C-G-G-G-C-G-T-Ψ-C-G-A-C-U-C-G-C-C-C-C-C-G-G-G-A-G-A-C-C-AOH

d) Phenylalanine tRNA:[9]

2Me DiH DiH DiMe 2'OMe 2'OMe

$_p$G-C-G-G-A-U-U-U-A-G-C-U-C-A-G-U——U-G-G-G-A-G-A-G-C-G-C-C-A-G-A-C-U-G-A-A-Y-A-

Me 7Me Me Me

...Ψ-C-U-G-G-A-G-G-U-C-C-U-G-U-G-T-Ψ-C-G-A-U-C-C-A-C-A-G-A-A-U-U-C-G-C-A-C-C-

...AOH

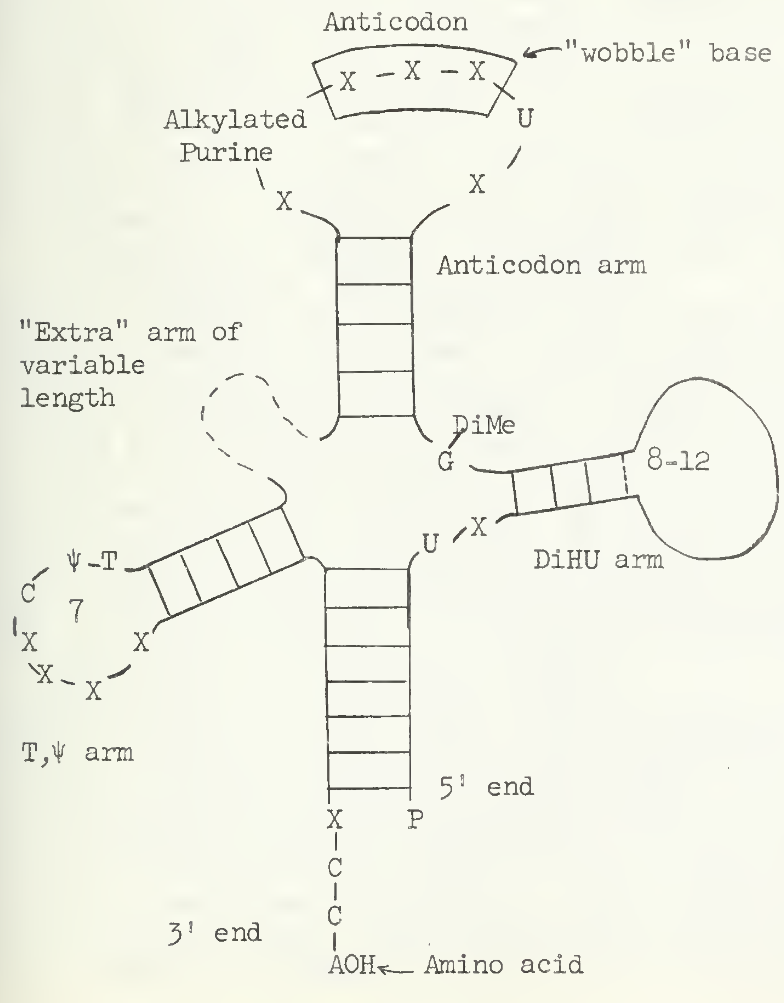
The nucleotide sequences of tRNA's that have been determined to date (Figure 2) confirm essentially all of the above conclusions and show several more common features. Significantly, all contain at least one sequence of three bases complementary (i.e., contiguous antiparallel) to the three bases constituting the mRNA codon for the corresponding amino acid; this sequence is referred to as the anticodon. In addition, there are the following common features: (1) no minor bases are found close to the acceptor end, (2) T is always the 23rd base from the acceptor end, (3) DiMeG is ninth base from the first base of the presumed anticodon, and (4) the presumed anticodon is preceded by U and followed by a minor base.

SECONDARY STRUCTURE--THE CLOVERLEAF MODEL

The cloverleaf model for the secondary structure of a tRNA was first put forward by Holley[4] as one of the possible secondary structures for alanine tRNA that utilize different regions of the RNA chain in Watson-Crick type base pairing. It was also pointed out that the conformation of tRNA's varies with the conditions; this, however, still leaves the biologically active conformation of tRNA's in question. A generalized cloverleaf structure is presented in Figure 3.

Since its presentation, a great preponderance of the evidence on the secondary and tertiary structure of tRNA's has accumulated in favor of a cloverleaf model. In view of the fact that all five tRNA's of known primary structure can be presented by an essentially identical secondary structure of the cloverleaf type, but not of an extended type, it would be difficult to dismiss this model. Even more compelling heuristic evidence is offered by the observation that in every known primary structure a potential anticodon sequence is found in the 3rd, 4th and 5th nucleotides of the loop distal to the acceptor end of the molecule. Moreover, the common trinucleotide sequence $T_p\Psi_pC_p$ is invariably found in the same loop in each case. This common sequence is believed to be involved in binding the amino acyl- or peptidyl-tRNA to the ribosome, since sufficient binding force is not provided by base-pairing at the anticodon site only.

Figure 3. Generalized Cloverleaf Structure[37] for Yeast tRNA's based on Sequences Determined for Alanine, Serine, Tyrosine and Phenylalanine tRNA's



Since early studies[10] with bulk and purified tRNA preparations on absorbancy-temperature profiles demonstrated the existence of a hyperchromic effect, which was reversed on rapid cooling, it was concluded that the tRNA's must possess intramolecular base pairing of the Watson-Crick type. Henely and co-workers,[38] using sedimentation velocity, viscosity and molecular weight data for yeast tRNA, calculated a ratio of major to minor axes of 7:1 for the unhydrated tRNA molecule; this ratio is incompatible with the cloverleaf model, where the four arms presumably extend in the form of an irregular tetrahedron. Vournakis and Scheraga[39] calculated theoretical ORD spectra

for alanine tRNA and tyrosine tRNA using the cloverleaf model and data obtained from studies of poly (G-C) and poly (A-U) double helices. Support for the cloverleaf model is afforded by the reasonably good agreement between calculated and observed spectra. On the basis of models that permitted maximization of the contributions of interbase hydrogen bonding and base-stacking interactions to the stability of the system, Cantor[40] proposed an alternate cloverleaf conformation with a more rigid tertiary structure. Ingram and associates[41] reasoned that the regions of the tRNA molecule that are most susceptible to attack by RNases under conditions that stabilize the native conformation are the nucleotide sequences most exposed in the native conformation. Partial digestion of alanine tRNA[33] and tyrosine tRNA[8] with RNase T_1,results in the cleavage of the molecules in half at the presumed anticodon site, indicating that this sequence is particularly exposed, an important requirement of a functioning anticodon site. In phenylalanine tRNA the presumed anticodon sequence is 2'OMeG-A-A; methylation at the 2'-O-position renders the associated phosphodiester linkage refractory to RNase T_1 hydrolysis without affecting the base-pairing properties of the nucleotide. Armstrong, et.al.,[41] observed that under defined digestion conditions RNase T_1 cleaved alanine tRNA first at the anticodon site and secondly removed a hexanucleotide from the acceptor end and cleaved in the DiHU loop. The common T-Ψ-C-G sequence was not cleaved under the conditions used, a finding hard to explain using the cloverleaf model. However, these studies support the existence of at least two loops. Englander and Englander[42] studied the isotope exchange behavior of mixed yeast tRNA. Only hydrogens involved in the hydrogen bonds exchange slowly enough for rate measurement. They found about 77 hydrogen bonds per average 70-nucleotide tRNA molecule,indicating the involvement of about 82% of the nucleotides. This observation supports the Cantor cloverleaf model somewhat better than it does the Holley cloverleaf.

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PROTON TRANSFERS IN AQUEOUS R_3NH^+-R_3N SYSTEMS

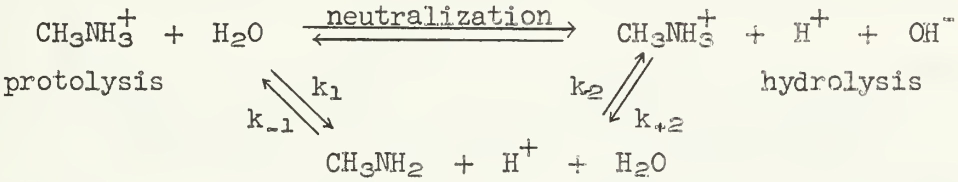
Reported by Stephen R. Byrn November 16, 1967

One of the steps in most acid and base catalyzed reactions is a proton transfer. For this reason proton transfers are of interest to organic chemists and an examination of the proton transfers in a model system, R_3NH^+-R_3N, will be presented.

Previous discussions of proton transfers include two seminars,[2,3] a review,[1] and several chapters in a book.[4] Since these discussions several new papers concerning R_3NH^+-R_3N systems have appeared. This seminar will deal with both these new papers and the older work with emphasis on the measurement of the rates of the reactions, and an attempt to determine the solvation of the reactants.

Since Eigen[1] has generalized the proton transfers one sees in acid-base systems and since our system is not extremely complicated, a discussion of the expected proton transfer reactions, and a method of calculating the encounter distance will be presented.

Choosing $CH_3NH_3^+$ as a model and applying Eigen's scheme for acid-base reactions gives the following results, where the names given to the reactions are descriptive.



The nmr method, as used by Grunwald, Loewenstein, and Meiboom, measures the lifetime (τ) of a proton on nitrogen.[18] Therefore, this method can only measure the rates of reactions involving transfer of a proton between $CH_3NH_3^+$ and a site of different magnetic environment. Thus, the rate constants k_1, k_{-1}, k_2, and k_{-2} can be measured, and the rates of the reactions in the neutralization equilibrium cannot be measured. It should also be noted that experimentally k_2 and k_{-1} are the same.

Two other reactions can also be measured by the nmr method. The broadening of

$$CH_3NH_3^+ + CH_3NH_2 \xrightarrow{k_3} CH_3NH_2 + CH_3NH_3^+$$

$$CH_3NH_3^+ + (H_2O)_n + CH_3NH_2 \xrightarrow{k_4} CH_3NH_2 + (H_2O)_n + CH_3NH_3^+$$

the H_2O line can be used to separate k_4 from the $(k_3 + k_4)$ obtained from the measurements of the lifetime of the proton on nitrogen.

The expected reactions from this examination of the model system, $CH_3NH_3^+$-CH_3NH_2, can now be written in generalized form, where B is any amine base.

$$BH^+ + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} B + H_3O^+ \qquad (1)$$

$$BH^+ + OH^- \xrightarrow{k_2} B + H_2O \qquad (2)$$

$$BH^+ + B \xrightarrow{k_3} B + BH^+ \qquad (3)$$

$$BH^+ + (H_2O)_n + B \xrightarrow{k_4} B + (H_2O)_n + BH^+ \qquad (4)$$

If the rate of any of these reactions is diffusion controlled the modified Smoluchowski equation could be used in a manner analogous to the case discussed below.

$$k_s = P\sigma \left[\frac{4\pi No(D_1 + D_2)}{1000} \right]$$

k_s = the measured rate
D_1,D_2 = diffusion coefficients of the reactants
σ = encounter distance
P = steric (orientation) factor (not in the original equation)[19]
N = 6.023×10^{23}

For the recombination of protons and hydroxide ions, assuming that P=1 Eigen

$$H^+ + OH^- \longrightarrow H_2O$$

calculated a σ of 7.5 ± 2 Å.[10] This large σ was explained in terms of the following mechanism:[16] (1) diffusive encounter of the hydrated ions $H_9O_4^+$ and $H_7O_4^-$; (2) formation of a hydrogen bond between these two hydrates; (3) "transfer" of a proton along the hydrogen bonded network. This "transfer" step involves the motion of charge by breaking an O-H bond and making an O-H bond out of an O-H hydrogen bond. This reaction is, therefore, the transfer of positive charge with a minimum of nuclear motion; (4) breakdown of the hydrates. Thus, the σ calculated, given the

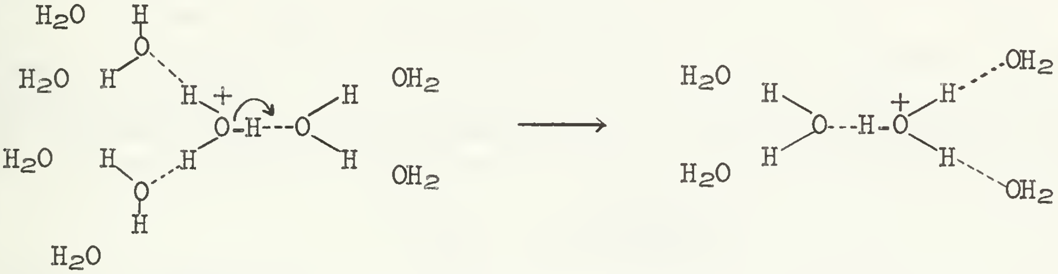


Figure 1. The Transfer of a Proton Through Water

rate constant and assuming P, may provide information concerning the solvation of the reactants.

The experimental determination of the rates of reactions (1) through (4) for $BH^+ = CH_3NH_3^+$ in aqueous acid (pH 3-5) will now be discussed.[18]

The rate of proton transfer may be written as follows, where τ is obtained from

$$\frac{1}{\tau} = k = \frac{\text{Rate}}{[CH_3NH_3^+]} = k_1 + k_2 \frac{K_W}{[H^+]} + (k_3 + k_4) K_{CH_3NH_3^+} \frac{[CH_3NH_3^+]}{[H^+]}$$

line width measurements of the CH_3 quartet and the other symbols have their usual meaning. A plot of $1/\tau$ vs. $[CH_3NH_3^+]$ at constant $[H^+]$ had an intercept of approximately 0; likewise, a plot of $1/\tau$ vs. $1/[H^+]$ at constant $[CH_3NH_3^+]$ had an intercept of approximately 0. Thus, k_1 and $k_2K_W/[H^+]$ are small compared to $(k_3 + k_4)$. It was found that $k_2K_W/[H^+]$ was insignificant in the acidic solutions discussed in this seminar.

A line width treatment of the broadening of the H_2O proton absorption gave k_4; thus, k_3 could be computed.

Luz and Meiboom[14] calculated n for reaction (4) where $BH^+ = (CH_3)_3NH^+$ using H_2O^{17} enriched water. The following reactions will contribute to the broadening of the proton lines of H_2O^{17} and the rate equation is written as follows, where the fractions

$$(CH_3)_3NH^+ + (H_2O)n + N(CH_3)_3 \xrightarrow{k_4} (CH_3)_3N + (H_2O)n + {}^+HN(CH_3)_3 \qquad (4)$$

$$H_3O^+ + H_2O \xrightarrow{k_5} H_2O + H_3O^+ \qquad (5)$$

$$H_2O + OH^- \xrightarrow{k_6} OH^- + H_2O \qquad (6)$$

are statistical factors and the symbols have their usual meaning. A plot of $1/\tau$ vs.

$$\frac{1}{\tau} = k = \frac{\text{Rate}}{[H_2O^{17}]} = \frac{1}{3} k_5[H^+] + \frac{1}{2} k_6 \frac{K_W}{[H^+]} + \frac{1}{2} n\, k_4 \frac{[Me_3NH^+][Me_3N]}{[H_2O^{17}]}$$

$\frac{1}{2}\frac{[Me_3NH^+][Me_3N]}{[H_2O^{17}]}$ had a slope of nk_4 and n was found, by dividing nk_4 by the k_4 obtained in H_2O^{16}, to be 1. It is probably reasonable to assume that n is 1 for all other B's.

Table I summarizes the values for the rate constants of reactions (1) through (4). Furthermore, Day and Reilly[6] have confirmed Grunwald's work by doing similar experiments on $(CH_3)_3ND^+$. The isotope effects are also consistent with the mechanisms proposed by Grunwald.

Table I** (25°)

BH^+	$k_1(sec^{-1})$	$10^{-10}k_{-1}(M^{-1}sec^{-1})$	$10^{-8}k_3(M^{-1}sec^{-1})$	$10^{-8}k_4(M^{-1}sec^{-1})$	$10^4K_B^*$
NH_4^+	25	4.3	11.7	0.9	0.18
$CH_3NH_3^+$	-	-	4.0	5.3	4.1
$(CH_3)_2NH_2^+$	-	-	0.5	9.0	6.0
$(CH_3)_3NH^+$	4.7	3.0	0.0	3.4	0.64
$(C_2H_5)_3NH^+$	-	-	-	1.8	6.5

*K_B is for free base.

**Composite of Table I ref. 5 and Table II ref. 7.

We will now consider the measurement of k_{-1} and k_1 in strong acid solutions ($pH<1$). The empirical rate equation for this reaction is shown below, where k and Q are empirical constants.[9]

$$\text{Rate} = \frac{k[BH^+]}{(1 + Q[H^+])}$$

A mechanism which explains these kinetics is:

$$B\mathcal{H}^{+}\cdot OH_2 + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} B\cdot\mathcal{H}OH + H_3O^+ \qquad (7)$$

$$B\cdot\mathcal{H}OH + H_2O \xrightarrow{k_H} B\cdot HOH + \mathcal{H}OH \qquad (8)$$

Assuming $[B\cdot\mathcal{H}OH]$ reaches a steady state one gets

$$0 = \frac{d[B\cdot\mathcal{H}OH]}{dt} = k_1[B\mathcal{H}^+\cdot H_2O] - k_{-1}[B\cdot\mathcal{H}OH][H^+] - k_H[B\cdot\mathcal{H}OH]$$

$$\text{Rate} = k_H[B\cdot\mathcal{H}OH] = \frac{k_1[BH^+]}{1 + \frac{k_{-1}}{k_H}[H^+]} \qquad (9)$$

Since $K_{BH^+} = k_1/k_{-1}$, and since k and Q in the empirical rate equation are identified with k_1 and k_{-1}/k_H in equation (9), we can calculate k_1, k_{-1}, and k_H. Calculation of these rate constants gave the values listed in Table I and showed that k_{-1} was the same order of magnitude as k_H. It should be noted that in $pH>3$ solutions $1 \gg k_{-1}/k_H[H^+]$ and equation (9) reduces to Rate = $k_1[BH^+]$, which is in agreement with the observed kinetics in solutions of this pH range.

Day and Reilly[6] found that $k_{1H}/k_{1D} = 6.7$ for $BH^+ = (CH_3)_3ND^+$ in D_2O($pD = 3-5$) by line width measurements on the methyl protons. The magnitude of this effect indicates that it is probably a primary isotope effect.

Grunwald[9] has conceived of the below alternatives to step (8). First, (8) could involve rotation of the H_2O molecule. It should be noted that $B\cdot\mathcal{H}OH$ and $B\cdot HO\mathcal{H}$ have an equal probability of reacting with a proton; thus, if (7) and (10) are the mechanism k in the empirical rate equation will be identified with $\frac{1}{2}k_1$, rather than k_1 (cf. mechanism (7) and (8)). A comparison of the value of k_1 for the

$$B\cdot\mathcal{H}OH \longrightarrow B\cdot HO\mathcal{H} \qquad (10)$$

imidazolium ion measured directly by the temperature jump method ($k_1 = 1.5 \pm 0.5 \times 10^3$ sec^{-1}, 13°C) to the k measured by the nmr method ($k = 2.4 \pm 0.4 \times 10^3$ sec^{-1}, 13°C) showed that k did not equal $\frac{1}{2}k_1$ but could equal k_1. Thus, a mechanism involving (7) and (10) was suggested to be unimportant.

A discussion of the errors involved in the measurement of rates by the two methods mentioned above will now be presented. The errors in the nmr method are rather unpredictable. Gutowski[21] has attributed the different $\Delta H^{\ddagger}$ values for the ring inversion of d_{11}-cyclohexane obtained in different laboratories to systematic error. It is, of course, impossible to determine whether the imidazolium ion experiments are subject to systematic error, but the possibility should be considered. Relaxation times can be measured within ± 10% by the temperature jump method.[22] A 30% error in k_1 was reported for the imidazolium ion; this is due to the complicated form of the relaxation time.[22] Accepting the 30% error in the temperature jump method and assuming a 30% error in the nmr measurements, rather than the 12% reported by Grunwald, gives us: $k_1(\Delta T) = 1.5 \pm 0.5 \times 10^3$ sec^{-1} and $k\ (\text{nmr}) = 2.4 \pm 0.8 \times 10^3$ sec^{-1}. Assuming that the contribution to k (nmr) from the rotation step (10) is $.7 \times 10^3$ sec^{-1}, one can suggest that the maximum contribution of the mechanism involving this step, (7) and (10), is about 30%.

Second, step (8) could be a Walden inversion. If this is the case k_H should

$$\text{HOH} + \text{B}\cdot\mathcal{H}\text{OH} \xrightarrow{k_{INV}} \text{HOH}\cdot\text{B} + \mathcal{H}\text{OH} \qquad (11)$$

equal k_{INV}. For dibenzylmethyl amine k_H was found to be four orders of magnitude greater than k_{INV}. Therefore, a mechanism involving (7) and (11) was ruled out, and the two step mechanism (7) and (8) was suggested to be the mechanism of reaction (1) in strong acid solutions.

It can also be seen from the above rate expression (9) that in extremely high acidities (>20% H_2SO_4) the rate equation reduces to the expression shown below where h

$$\text{Rate} = K_{BH^+}\, k_H \frac{[BH^+]}{[H^+]} = k_H\, h \qquad\qquad h = \frac{A_{H^+}\gamma_B}{\gamma_{BH^+}}$$

is the appropriate acidity function.* Therefore, from acidity functions and the measured rate one can examine medium effects on k_H. It was found that k_H was a constant over a six-fold range of viscosity.[9] This was taken to mean that the solvation shell of B did not involve cooperation of a substantial number of solvent molecules; for, if a large number of solvent molecules were involved, stepwise changes of k_H would be expected to be seen as the solvent composition is changed. It was suggested, on the basis of the independence of k_H on viscosity, that only the water molecule adjacent to the free electrons of B was greatly different from the molecules of bulk solvent- that is, there is no "iceberg" type solvation of B.

A short examination of acidity functions and their meaning is pertinent to the above assumption that appropriate acidity functions are available. For $B=CH_3NH_2$ the acidity function for anilines h' was used, and for $B=(CH_3)_3N$ the acidity function for tertiary anilines h''' was used. These acidity functions are empirically measured for the prescribed series of amines and are defined in the usual manner. Arnett, in a discussion of the applicability of acidity functions, points out that h may be extremely sensitive to the structure of the base and that indiscriminate use of acidity functions is dangerous.[20] Therefore, the use of these functions to examine the relationship of k_H to viscosity may introduce substantial errors.

Let us now discuss diffusion controlled reactions, and the calculation of the encounter distance of the reactants with the Smoluchowski equation. Of special interest will be the reaction with the rate k_{-1}. This reaction is probably diffusion controlled, since the difference in k_{-1} for $B=NH_3$ and $B=(CH_3)_3N$ is proportional to the difference in diffusion coefficients of these two species.

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*It should be noted that $H = -\log h$

Table II gives values of P and σ for selected diffusion controlled reactions. For the reaction of protons with hydroxide ions and for the reaction of ammonia with

Table II

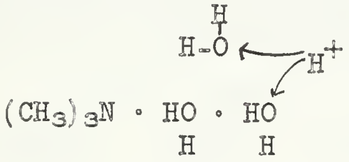
Reaction (H_2O solvent unless noted)	10" k ($M^{-1}sec^{-1}$)	P	σ(Å)	Ref.
$H^+ + OH^- \rightarrow H_2O$	1.4	1^{**}	7.52	10
$NH_3 + H^+ \rightarrow NH_4^+$	0.43	1^{**}	4.85	11
$H^+ + F^- \rightarrow HF$	1.0	1	7.5^*	13
$H^+ + SH^- \rightarrow H_2S$	0.75	3/4	7.5^*	13
$(CH_3)_3N + H^+ \rightarrow (CH_3)_2NH^+$	0.30	$P\sigma = 3.2$		12
$(CH_3)_3N + H^+ \rightarrow (CH_3)_3NH^+$ (MeOH solvent)	0.06	$P\sigma = 1.5$		12

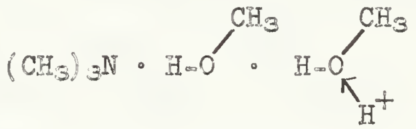
*Assumed to calculate P
**Assumed to calculate

protons P was assumed to be one and σ calculated. For the reactions of hydrosulfide and fluoride ion with protons σ was assumed to be 7.5 Å and P calculated. An examination of the values of P in this table is rather confusing since if P = 1 for F^- one would expect that P would equal 3/4 for OH^- and SH^- and 1/4 for NH_3- that is, P is the number of sites available for proton transfer divided by the total number of sites.

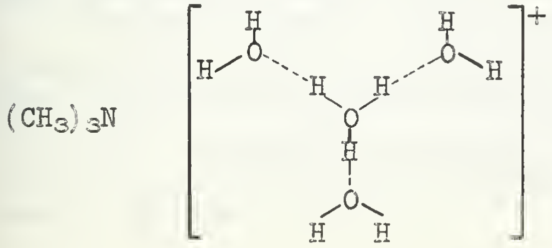
The reactions of nitrogen bases with protons will now be discussed in an attempt to discover why there is confusion in the values of the orientation factor P. If one assumes that P = 1/4 for the reaction of ammonia with protons a σ=20 Å is obtained. This is unreasonably large for the reaction of an ion and a neutral species.[11] On the other hand, a σ=4.85 Å is reasonable for proton transfer every time the reactants become next nearest neighbors. Grunwald explained that P is effectively one because the diffusing molecules are oriented by the molecular fields (dipole-dipole interaction) as they approach each other.[11] An alternate explanation assuming that the rate of NH_3 rotation is faster than the average encounter time can be ruled out on the basis of the imidazolium ion experiments. Eigen has explained the apparent discrepancy in the values of P for OH^- and SH^- by a similar orientation by molecular fields.[1]

The difference in Pσ for $(CH_3)_3N$ in H_2O and in CH_3OH was explained by Grunwald[12] as follows:

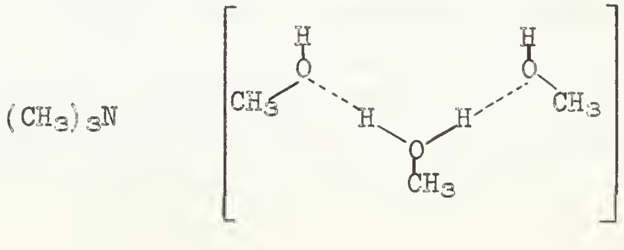




Thus, in water (tetrahederal solvation), assuming that solvated trimethyl amine reacts with unsolvated protons, the reaction is favored by a factor of two over the reaction in methanol (linear solvation). One would, however, expect that the proton is the solvated species, from analogy to the work of Eigen, and that NH_3 and $(CH_3)_3N$ are unsolvated or solvated by one water molecule as discussed above. Attempting to explain the different P values assuming the proton is solvated yields a factor of three as shown below.



6 free protons



2 free protons

Although we have explained the unexpected values of P for the reactions of OH^- and NH_3 with protons the explanations presented above are not entirely adequate. This inadequacy may be attributed to the failure of the modified Smoluchowski equation. Support for this suggestion comes from at least two arguments: (1) In the Smoluchowski treatment the reaction of a neutral species and an ion and the reaction of two neutral species are governed by the same equation; thus, solvation effects are completely neglected and large errors are possible. (2) Marcus[17] has pointed out that modification of the Smoluchowski equation by a factor to account for reaction inefficiency (e.g. the orientation factor P) is theoretically unfounded since, by definition, this reaction is no longer diffusion controlled. Therefore, it was suggested that instead of using this factor the reaction should be treated as a diffusion-activation controlled reaction as shown below, where the observed reaction time is made up of both an activation time and a diffusion time.

$$\frac{1}{k_{obs}} = \frac{1}{k_{act.}} + \frac{1}{k_{diff.}}$$

It is also possible that the values used for k in the Smoluchowski equation are in error.

Reaction (3) will now be discussed. This reaction involves direct proton

$$BH^+ + B \rightarrow B + BH^+ \qquad (3)$$

transfer and therefore requires that all solvation structure be destroyed before reaction. Grunwald[12] has pointed out that it is difficult to tell whether this reaction is diffusion or activation controlled. The activation parameters for (3) where $B=CH_3NH_2$ are $E_a=16 \pm 454$ cal/mole, $\Delta H^\ddagger = -580$ cal/mole, $\Delta G^\ddagger_{25} = 5{,}310$ cal/mole and $\Delta S^\ddagger = -19.8$ eu.[8] Loewenstein does not use these parameters to answer the question of diffusion or activation control, but merely points out that E_a for the reaction of H^+ with OH^- is about 2 kcal/mole and that such a low E_a is unexpected.

Further conclusions about the mechanism of (3) are limited to the observation that k_3 decreases as methyl substitution increases, which was taken to mean that there is either increased steric hinderance in the transition state as methyl groups are added, or that the energy of desolvation increases as methyl groups are added.[5] Further experiments of some sort are needed to elucidate the details of this reaction.

Reaction (4) was found to involve one water molecule. Meiboom suggested that

$$BH^+ + H_2O + B \xrightarrow{k_4} B + H_2O + {}^+HB \qquad (4)$$

the water molecule involved belongs to the solvation shell of the BH^+.[14] It should also be noted that in other reactions involving an ion and a neutral species a reaction involving one water molecule was found. This indicates that the involvement

$$PhOH + H_2O + {}^-OPh \rightarrow PhO^- + H_2O + HOPh^{15}$$

$$PhCOOH + MeOH + {}^-OOCPh \rightarrow PhCOO^- + MeOH + HOOCPh^{14}$$

Ph = phenyl

of one molecule of solvent in proton transfers between ions and neutral species is fairly common.

The rate of k_4 increases with respect to k_3 as methyl groups are substituted for hydrogens. This trend could be taken as a reflection of either steric or solvation factors, or both. Further experiments are also necessary to elucidate the importance of these factors, as was the case with k_3.

The rate k_4 varies linearly with K_{BH^+}. Triethyl amine, however, falls off this straight line. This was explained by steric hinderance in the transition state. The rate k_4 does not vary linearly with gK_{BH^+} (g = statistical factor, e.g. g = 4 for NH_4^+). Grunwald has commented in a footnote that the failure of this correlation may be due to different g's for the solvated ion and the relatively unsolvated neutral species.

In conclusion, if one accepts the R_3NH^+-R_3N system as a model for proton transfer reactions which occur in aqueous acid or base catalyzed reactions, then participation of solvent in these reactions plays an important but relatively unknown role.

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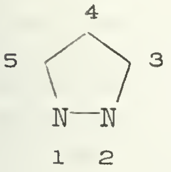
MECHANISTIC CONSIDERATIONS OF THE PYROLYSIS OF PYRAZOLINES

Reported by Craig Marken November 20, 1967

INTRODUCTION

There has been considerable debate in the recent literature over the mechanism of the thermal decomposition of pyrazolines. For the most part this uncertainty in the mechanism is derived from the stereochemical outcome of the formation of the substituted olefin and cyclopropane products obtained in these decompositions. Reviews on the earlier work concerning the general synthesis of substituted pyrazolines and their decomposition have been covered[1,2,3] and, therefore, this seminar will be primarily concerned with the advances made since 1962 which help clarify the mechanisms involved. Pyrazoline is a five membered ring having two adjacent nitrogens with a double bond in the 1 or 2 position and a numbering system as shown. There have been two mechanisms suggested as early possibilities for the formation of olefins and cyclopropanes by pyrolysis of pyrazolines. One involves an ionic or dipolar intermediate[4] and the other a diradical intermediate.[5] It will be shown that no one mechanistic scheme is suitable to explain the many and varied results and that it is possible that a clear distinction between dipolar and diradical intermediates may not necessarily be used as an explanation. The mechanism may be between these two extremes depending on substituents and reaction conditions.

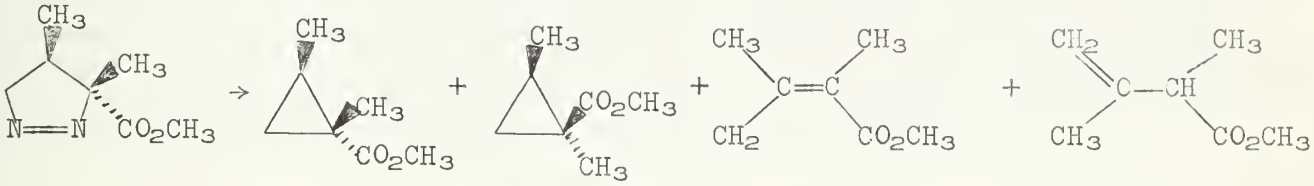


BACKGROUND

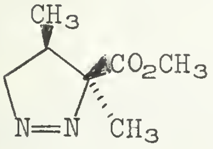
Early evidence suggested that the formation of cyclopropanes from the thermal decomposition of pyrazolines was a stereospecific reaction with the geometry of the products being identical to the geometry of the initial pyrazolines.[6] Later investigations[7,8] revealed that some decompositions of pyrazolines lead to a non-stereospecific formation of substituted cyclopropanes. However, some of the analytical determinations in some of this early work has been found to be in error[9,10] and some of the structural determinations were based on the stereospecificity of the thermal decomposition of pyrazolines. In the more recent work the stereochemical outcome of this type of decomposition has been more precisely investigated.

MECHANISTIC CONSIDERATIONS

In an investigation of the thermal decomposition of neat cis and trans-3-carbomethoxy-3,4-dimethyl-1-pyrazoline (1 and 2) Rinehart[9] reported that cis and trans-1-carbomethoxy-1,2-dimethylcyclopropane (3 and 4) are formed in almost equal amounts from each starting material as follows:



1	3	4	5	6
	1.00	0.70	3.73	0.24



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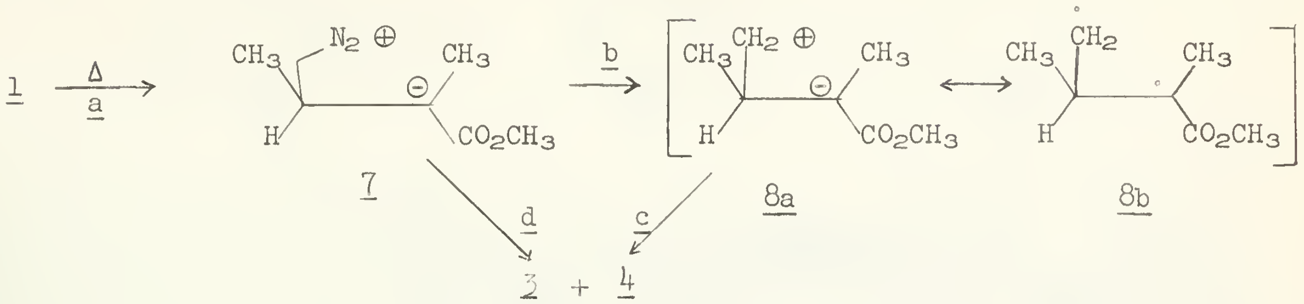
→ 3	+ 4	+ 5	+ 6
1.00	1.22	1.16	0.15

Although there is some loss of geometry the results show a preference for the retention of configuration of the original pyrazoline in the cyclopropanes.

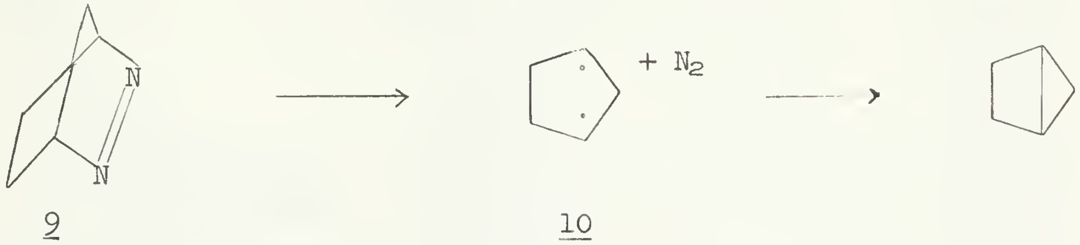
The above results could be explained[9] by an elaboration of the proposed[4] mechanism by using 1 as an example. Before cyclization, rotation about the C_3 and C_4 bond must



take place either in species 7 or 8 if there is to be any loss of geometry. Step d should have a lower energy of activation than step b but because of the orientation required at C_4-C_5 for a back side displacement of nitrogen on C_5, the entropy factor makes this unfavorable. If the negative charge of species 7 is delocalized into the carbomethoxy group, the C_3 carbon should be close to planar. The barrier to rotation in this species should be greater than that of the eclipsing methyls in butane which is estimated[11] to be 4.4 to 6.1 kcal. mole^{-1}. Since the energy of activation for the formation of the primary carbonium ion similar to step b has been estimated[12] to be 3-5 kcal. mole^{-1}, the barrier to rotation should be greater than the activation energy of step b and loss of nitrogen should be favored over rotation. Thus some stereoselectivity would not be surprising. The zwitterion (8a) having some resonance contribution in the form of a singlet diradical (8b), could then undergo an immediate cyclization to form the cyclopropane products. The olefin products result from a hydrogen transfer in intermediate 8.

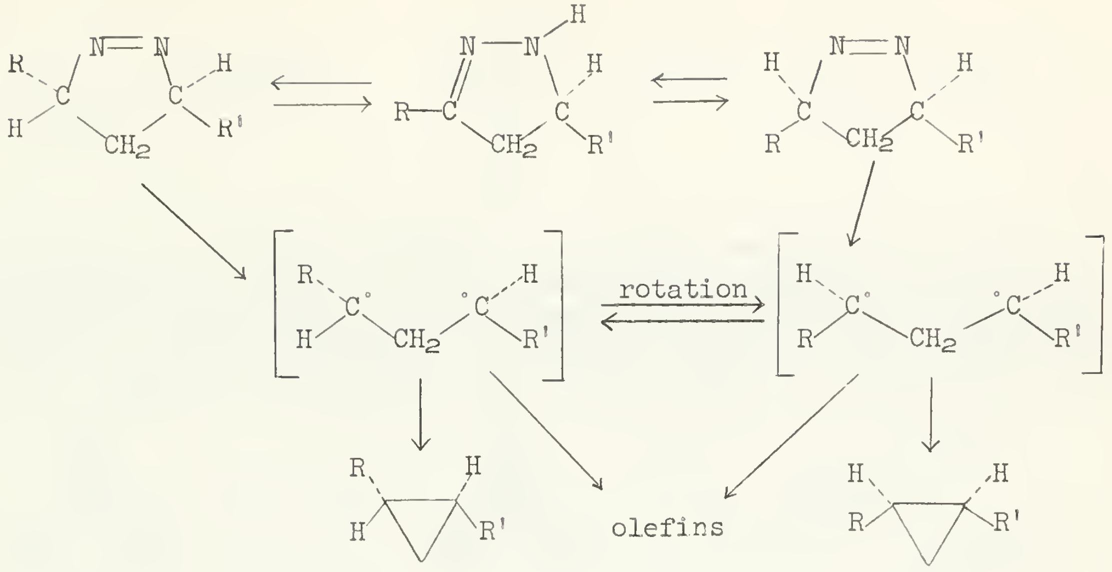
The stereoselectivity of the intermediate could be influenced by a combination of two competing factors. First, increasing the steric size of the substituents would hinder rotation about the carbon-carbon bonds and thus increase stereoselectivity. Second, increasing the stability of the intermediate through delocalization would increase the lifetime of the intermediate and thus decrease stereoselectivity. A combination of these factors could cause a wide variety of results.

Some early work presented evidence for a diradical intermediate upon pyrolysis of a pyrazoline system in solution. Cohen[13] conducted a kinetic investigation on 2,3-diazabicyclo[2,2,1]-2-heptene (9) and observed excellent first-order kinetics with an activation energy, $E_a=37.3\pm0.3$ kcal. mole^{-1} and an entropy of activation $\Delta S^*=8.7\pm0.4$ e.u. For a comparison azo-bis-2-propane[14] has an energy of activation of 40.9 kcal. mole^{-1} and acyclic azo-compounds[15] have entropy activation values in the range of 12 to 15 e.u. Deviations from the energy of activation of acyclic compounds probably arises from relief of strain in the bicyclic structure 9 and that of entropy of activation may be in the formation of a nitrogen molecule and one diradical (10) rather than a nitrogen molecule and two radicals.



Overberger[16,17] also suggested that a diradical mechanism is operative for the thermal decomposition of 3,5-diaryl-1-pyrazolines in the stereospecific formation of substituted cyclopropanes in benzene solution.

The following scheme was used to explain the results that trans-pyrazolines, where the aryl groups were phenyl, p-methoxyphenyl of p-chlorophenyl, formed nearly quantitatively trans-cyclopropane and in cis-pyrazoline, where the aryl group was p-methoxyphenyl, the cyclopropane products were 57% trans-configuration. In order



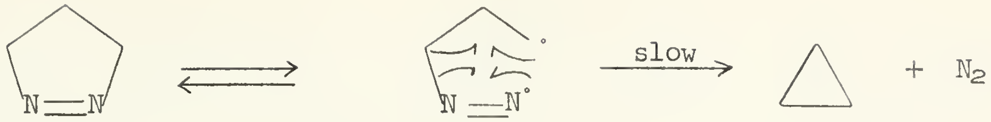
to explain the results, Overberger[18] suggested that fast closure of the diradical intermediate by the close proximity of the radical centers forms the thermodynamically more stable trans cyclopropane. Electronic effects had little to do with these results since all of the rates were very closely the same.

Work on the thermal decomposition of pyrazoline in the vapor phase in which there was no possibility of delocalization of electrons either by electronegative carboalkoxy groups or by aromatic substituents was conducted by Crawford.[19] First order kinetics were observed for 3- and 5-methyl substituted pyrazolines. Decreases in ΔS^*(see Table I) upon greater substitution of methyl groups would be expected if the transition state more closely resembles the starting material as a di-tertiary species is approached. Owing to the change of the energy of activation upon substitution of methyl groups on the 3- and 5-position, it was suggested that both carbon-nitrogen bonds were broken simultaneously.[21,22] Since the observed energies of activation of cis and trans 3,5-dimethyl-1-pyrazolines (11 and 12) are less than that for 3-methyl-1-pyrazoline while those for 3,5,5-trimethyl-1-pyrazoline and 3,3,5,5-tetramethyl-1-pyrazoline are less than 3,3-dimethyl-1-pyrazoline it can be argued that both carbon-nitrogen bonds are cleaved simultaneously in the transition state. Therefore

Table I

Substituent	E_a(kcal. mole^{-1})	ΔS^* e.u.
none	42.4 ± 0.3	11.2 ± 0.6
3-methyl	41.0 ± 0.3	10.5 ± 0.7
4-methyl	42.2 ± 0.2	10.8 ± 0.5
3,3-dimethyl	40.0 ± 0.2	10.8 ± 0.4
3,5-dimethyl (cis)	40.3 ± 0.3	9.4 ± 0.5
3,5-dimethyl (trans)	40.2 ± 0.3	10.0 ± 0.5
3,3,5-trimethyl	38.9 ± 0.4	8.9 ± 0.6
3,3,5,5-tetramethyl	37.7 ± 0.4	4.6 ± 0.7
9	36.9 ± 0.3	5.7 ± 0.4

the intermediate was suggested to be a trimethylene type diradical which forms the cyclopropanes and olefins. While kinetic evidence cannot rule out an intermediate such as 13 it can be considered unlikely since the partial reaction of either 11 or 12 does not yield a mixture of both isomeric pyrazolines.



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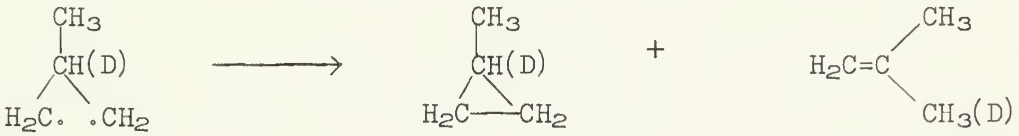
Kinetic studies on 4-deuterio-4-methyl-1-pyrazoline revealed that the rate parameters are identical to those for the non-deuterated analogue but the product ratios are changed. This suggested that an intermediate is involved (species 14 is suggested) which precedes hydrogen (or deuterium) migration as the product determining step with a $k_H/k_D = 1.80$ assuming the isotope effect in ring closure is unity.



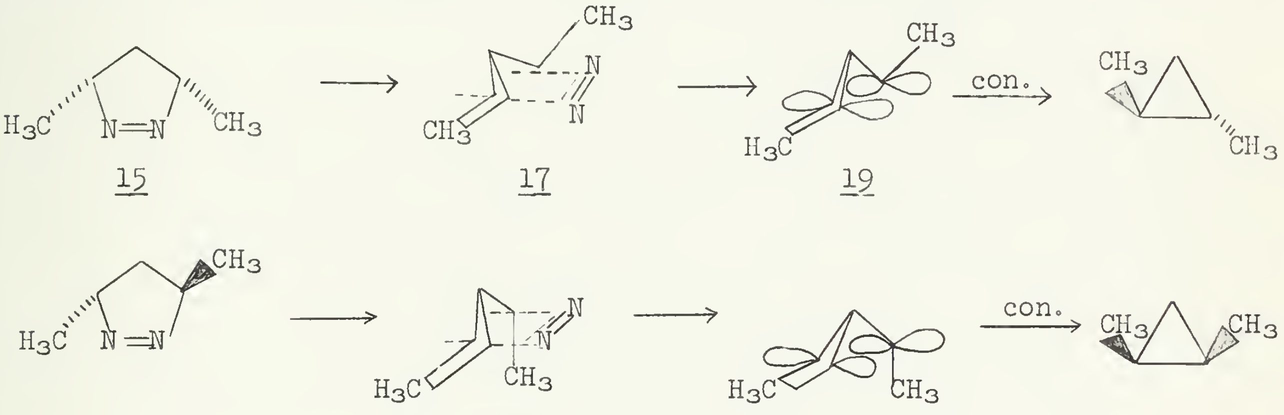
14 22

The stereochemical outcome of this decomposition[22] was investigated with the *cis* and *trans*-3,5-dimethyl-1-pyrazolines (15 and 16). The results are shown in Table II.

Table II

Pyrazoline	1,2-dimethylcyclopropane		2-pentene	
	cis %	trans %	cis %	trans %
15	33.2±0.6	66.1±0.6	0.0	0.68±0.08
16	72.6±0.4	25.4±0.6	0.92±0.11	1.08±0.17

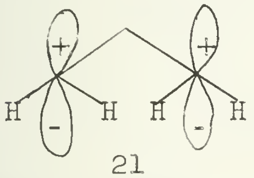
The results show that the decomposition of 15 and 16 proceeds through a different transition state and intermediate as shown below. The predominant inversion of configuration observed in the products (see Table II) can be explained by the conrotatory mode of rotation of the intermediates 19 and 20 while the minor cyclopropane product can be explained by a disrotatory mode of rotation. The olefin can be explained by hydrogen migration. The transition states are supported by kinetic data of 4-methyl and 4,4-dimethyl-1-pyrazoline which suggest some steric inhibition of rates of decomposition assuming a transition state similar to 17 and 18. The rate of decomposition for 1-pyrazoline is 16.0×10^{-4} sec^{-1} while those for 4-methyl-1-pyrazoline and 4,4-dimethyl-1-pyrazoline are 15.5×10^{-4} sec^{-1} and 0.126×10^{-4} sec^{-1} respectively. These rates show almost no change in rate upon substitution of one methyl group but more than a hundred-fold decrease in rate upon substitution of a second methyl group in the 4-position.



15 17 19

16 18 20

The intermediates, such as 19 and 20, may be considered as diradical but the products which they stereoselectively form suggest that the terminal methylenes are not independent of each other.[21] It is suggested that this influence could be overlap between the two p-orbitals on the terminal methylenes to form a "π_g-cyclopropane" (21). There are three terms that influence this species: 1) angle strain, 2) π-bond energy and 3) hydrogen nonbonding repulsion. In a calculation[23] of these terms it was suggested that there is a barrier to rotation between the pyrazoline C_3 and C_5 because of a π-overlap bond energy of about 8-12 kcal. mole^{-1}. These calculations suggest that there is an energy of activation for the formation of cyclopropane products. Hoffman[24,25] has conducted extended Hückel calculations on the CH_2-CH_2-CH_2 species. They involved the energy as a function of C-C-C angle and rotation of the terminal methylene groups. The ground state calculations reveal two minima on a potential surface. One of these minima is for cyclopropane while the other, surprisingly enough, is a shallow minimum for a "π_u-cyclopropane" (22). The π_u-cyclopropane is a singlet with both electrons in an antisymmetric orbital. The same calculations for the excited state reveal a broad minimum on the potential surface, for a "π_g-cyclopropane" (21), which allows the terminal methylenes to be freely rotating. The π_u-cyclopropane is capable of conrotatory ring closure while the ring closure for the π_g-cyclopropane is of the disrotatory mode and an equilibrium[21] could control the ratio of cis and trans cyclopropane products. Hoffman's calculations support the observations of Crawford since they show a preference for the conrotatory mode over the disrotatory mode of rotation. Attempts to trap such an intermediate by a thermal ring closure with an olefin has failed to alter the course of the reaction.



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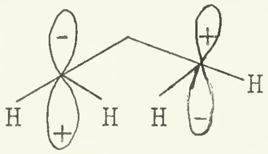

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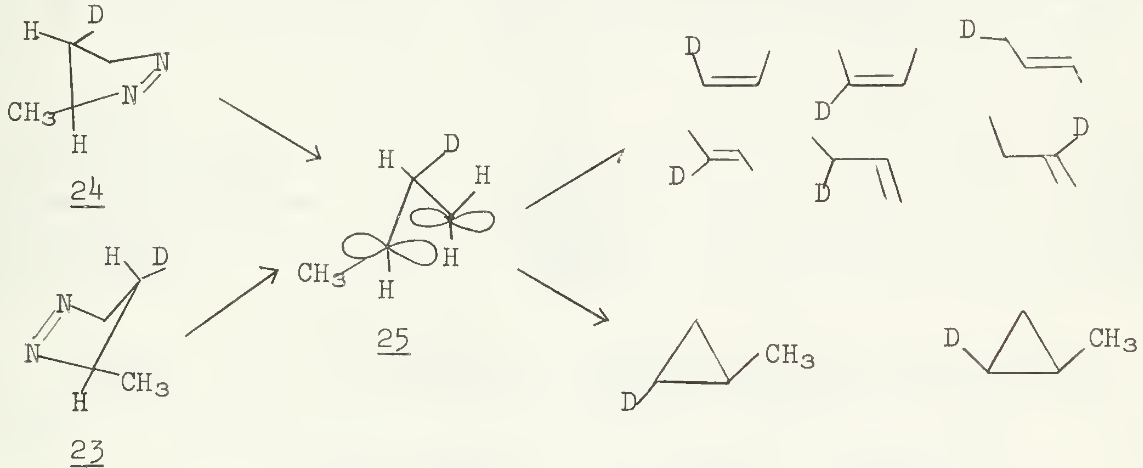
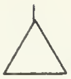
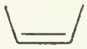
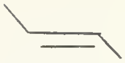
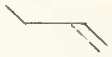
Crawford[26] presents evidence to substantiate the theory that the trimethylene intermediate is a planar species which is free from nitrogen and its influence. If it is assumed that the above intermediate has sufficient lifetime to become a nitrogen free species, then cis and trans 4-deuterio-3-methyl-1-pyrazoline (23 and 24 respectively) should yield an identical intermediate (25). If such a species

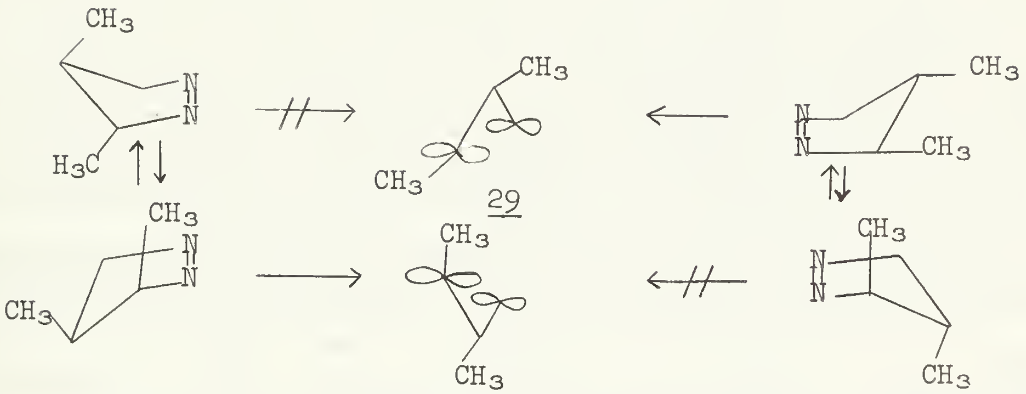


exists the ratio of products will be independent of its origin. Using the product ratios for undeuterated 3-methyl-1-pyrazoline (26) and a k_H/k_D ratio of 2.0 in the product determining step[20] to determine the product ratios it was found that both 23 and 24 gave the ratio of products as predicted (see Table III).

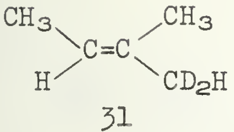
The secondary isotope effects in the decomposition of cis and trans-3,4-dimethyl-1-pyrazoline (27 and 28) have been used to demonstrate that both carbon-nitrogen bonds are broken in the rate determining step supporting the possibility of the proposed transition states (29 and 30).[27] Steric inhibition would cause a preference in the formation of the intermediates, i.e., 27 would favor 30 and 28 would favor 29. This was verified using 1,1-dideuterio 27 and 28 which afforded 31 and 32 respectively.

Table III

				
26	93.3±0.6 %	1.9±0.2 %	1.16±0.12 %	3.7±0.3 %
calculated	94.9	1.4	0.9	2.8
23	95.1±0.5	1.4±0.2	1.0±0.1	2.5±0.3
24	94.7±0.5	1.5±0.2	1.1±0.2	2.7±0.3

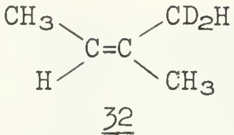


27 30 28



$$\begin{matrix} CH_3 & & CH_3 \\ & C{=}C & \\ H & & CD_2H \end{matrix}$$

31



$$\begin{matrix} CH_3 & & CD_2H \\ & C{=}C & \\ H & & CH_3 \end{matrix}$$

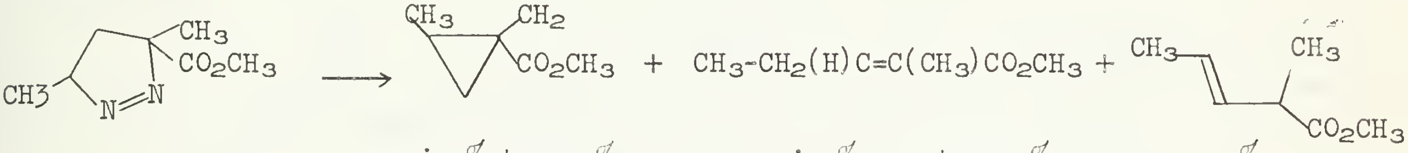
32

Along with these results it was shown that the cyclopropane products were formed non-stereospecifically about the C_3-C_4 bond of the pyrazoline as shown in Table IV.

In continuing the investigation of the mechanism of the pyrolysis of pyrazolines, McGreer[28,29] has decomposed cis- and trans-3,5-dimethyl-3-carbomethoxy-1-pyrazoline (33 and 34) with the intention of studying the olefin formation. The results shown are for the vapor phase reaction. When the reaction is in solution, there is a solvent effect which increases the amount of olefins with increasing dielectric constant but without changing the stereochemistry. However, there is no increase in the rate of reaction with this change of solvent and even some possibility of a slight decrease. Olefin formation was found to be more stereospecific than cyclopropane formation with cis olefin being formed from trans 34 and the trans olefin from 33. Also an inversion of the relative geometry was noted during the formation of cyclopropane.

Table IV

Product	27	28
cis-dimethylcyclopropane	45.4±0.1 %	46.0±0.5 %
trans-dimethylcyclopropane	33.0±0.6	21.8±0.3
2-methyl-2-butene	14.3±0.3	16.3±0.3
2-methyl-1-butene	7.2±0.4	15.8±0.2

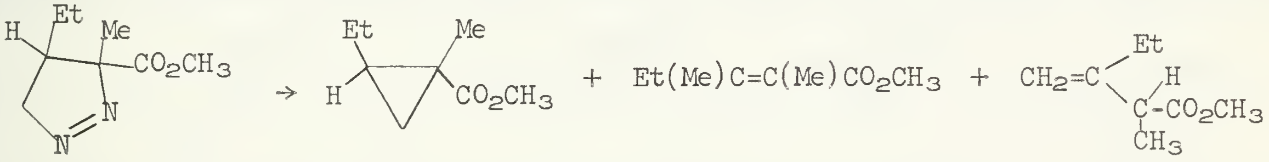


	cis %	trans %	cis %	trans %	%
cis 33	23	65	2	5	5
trans 34	76	15	3	1	5

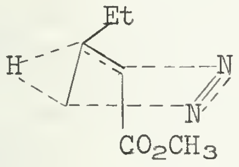
The mechanism presented by Rinehart was discounted in this case for two reasons. First, if the lifetime of the intermediate (i.e., like 8) is sufficiently long to

permit free rotation, it could be expected that a reversal of the initial step would lead to an isomerization of the two pyrazolines. Second, because of the planar nature of the C_3 carbon caused by delocalization, the intermediate would be independent of the starting material. The results indicate that neither of the two conditions were observed. However, Rinehart[9] also indicates that no isomerization of the initial pyrazolines was detected. Since the ratio of cyclopropane to olefin changed with solvent, McGreer suggested that these two products are formed through slightly different transition states in which the olefin forming state would be more polar. Owing to the fact that the pyrazoline ring is not planar, the olefin forming transition state could involve a hydrogen migration concerted with nitrogen elimination, where the migrating hydrogen is trans to the leaving nitrogen. Since this transition state would be less polar than the ring-opened dipolar intermediate, a concerted process was suggested as a possible pathway to cyclopropane formation. Retention of the pyrazoline geometry would result if the nitrogen would leave in the plane of the three carbon atoms while inversion of geometry would result if the nitrogen would leave perpendicular to the three carbons. In the latter case, steric interference of substituents at C_3 and C_5 could result in inversion of one of the carbon atoms.

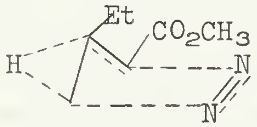
Through the use of 35 and 36, McGreer[30] further tried to clarify the pathway of olefin formation from pyrazolines. The data show that α-β-unsaturated esters were formed stereospecifically. If a concerted hydrogen migration and nitrogen elimination occurs as in the transition states 37 and 38, which indeed predict the correct olefins, then the advantage of this pathway must be able to overcome the preferred pseudo-axial conformation of the C_4 ethyl group. This transition state will predict the olefin formation in Crawford's work.[19,21,22] However, Crawford[21] calculates through the use of deuterium isotope effects on 4-deuterio-4-methyl-1-pyrazoline that a system involving different intermediates for olefin and cyclopropane formation is highly improbable.



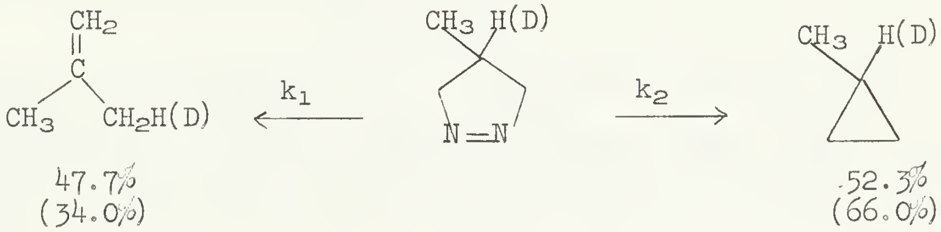
	cis %	trans %	cis %	trans %	%
cis (35)	47	19	0	29	6
trans (36)	18	74	6	0	2



37



38

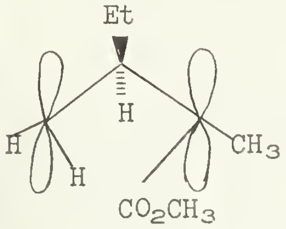


$$k_{obsH} = k_{1H} + k_{2H} \qquad k_{obsD} = k_{1D} + k_{2D}$$

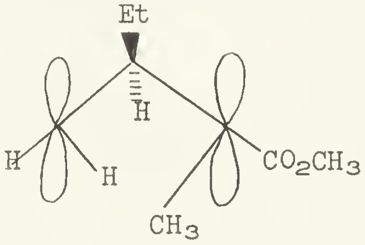
$$\frac{k_{obsH}}{k_{2H}} = 1 + \frac{k_{1H}}{k_{2H}} = 1.91 \qquad \frac{k_{obsD}}{k_{2D}} = 1 + \frac{k_{1D}}{k_{2D}} = 1.51$$

$$\frac{(k_{obsH})(k_{2D})}{(k_{obsD})(k_{2H})} = 1.27 \qquad \frac{k_{obsH}}{k_{obsD}} = 1.07$$

This yields a value of $k_{2H}/k_{2D} = 0.84$ which indicates a rate of ring closure increase of 15% by deuterium substitution which is unlikely. There are a few discrepancies in applying McGreer's results to Crawford's π-cyclopropane intermediate.[30] If the correct olefins are to be formed, 35 will have to proceed through 39 while 36 will go *via* 40. However, for this to happen the nitrogen elimination must be from the most hindered side, which is unlikely. If the correct π-cyclopropane, 39, were formed from pyrazoline, 35, experimental results show that the two bulkier groups (ethyl and methyl) end up *cis* to each other which is similar to results observed by Crawford.[27]

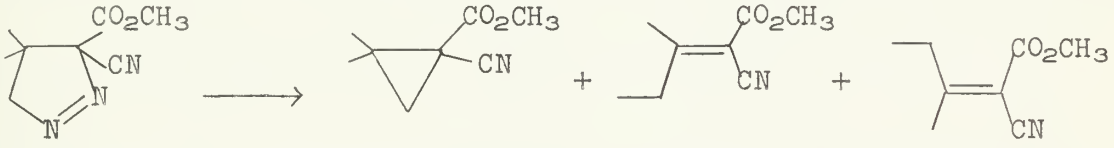


39



40

McGreer[31] also investigated the possibility of an ionic intermediate. To obtain an ionic intermediate 4,4-dialkyl-3-cyano-3-carbomethoxy-1-pyrazolines were used because of the electron withdrawing groups on C_3. Since it was thought that if a positive charge were developed on C_5, the alkyl group would migrate to that carbon forming a more stable positive charge on a tertiary carbon. As predicted, the alkyl groups did migrate in the many cases tested as shown in the example. There was also an increase in the rate of nitrogen evolution upon increasing the polarity of solvent. This is in contrast to Crawford's work[21] in which there was no olefin formed by methyl migration in 4,4-dimethyl-1-pyrazoline, but the formation of 2-methylpropene was observed as one of the products.



CONCLUSION

Since it appears that no one mechanistic scheme will completely explain the many and varied results, it is not exactly clear that either a diradical or a dipolar mechanism will be the correct description, but it may be somewhere between the two extremes of the spectrum depending on resonance contributions which could vary under the influence of solvents, reaction conditions and substituents. For example,[28] both carbon-nitrogen bonds may be breaking simultaneously in the transition state while some substituted pyrazolines may show unequal bond breaking. In solution there may be more than one mechanism existing. It can be concluded that thermal decomposition of pyrazolines is not as stereospecific as originally believed in both cyclopropane and olefin formation. It is not reliable to make predictions and structural determinations from this reaction.

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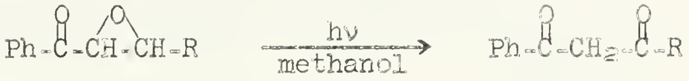
MECHANISTIC ASPECTS OF THE PHOTOCHEMICAL REARRANGEMENTS OF α,β-EPOXYKETONES

Reported by Charles R. Payet November 30, 1967

A number of studies have contributed to the understanding of the mechanisms of the photochemical reactions of α,β-epoxyketones. This seminar will summarize the results of these investigations. Other reviews[1-3] have catalogued the reactions of the α,β-epoxyketones.

REARRANGEMENTS TO β-DIKETONES

In 1918 Bodforss[4] reported that the α,β-epoxyketone 1 photochemically isomerized to the 1,3-diketone 2. The proton was the migrating species in all the reactions.

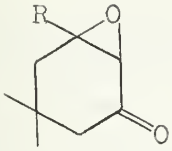


$$\text{Ph-}\overset{O}{\overset{\|}{C}}\text{-}\underbrace{\text{CH-CH}}_{}\text{-R} \xrightarrow[\text{methanol}]{h\nu} \text{Ph-}\overset{O}{\overset{\|}{C}}\text{-CH}_2\text{-}\overset{O}{\overset{\|}{C}}\text{-R}$$

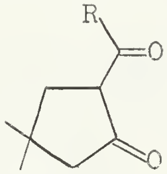
1 0.5 hr 2

R = Ph, m-NO_2-Ph, p-Cl-Ph

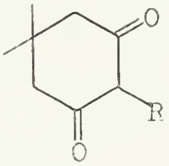
In a more recent study Reusch and coworkers[5] found that the preferential migration of alkyl rather than aryl groups was characteristic of β-diketone formation. Isophorone oxide (3) photochemically isomerized to give a 9:1 mixture of 2-acetyl-4,4-dimethylcyclopentanone (4) and 2,5,5-trimethylcyclohexane-1,3-dione (5); however, when 3-phenyl-5,5-dimethyl-2,3-epoxycyclohexanone (6) was irradiated only the 2-benzoyl-4,4-dimethylcyclopentanone (7) was produced.



3, R = CH_3
6, R = Ph



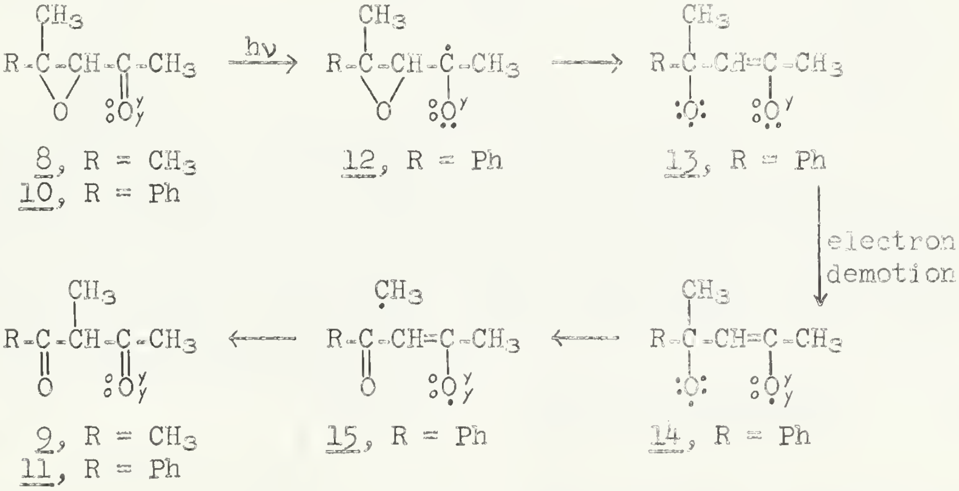
4, R = CH_3
7, R = Ph



5, R = CH_3

Reusch and associates[5] reported that 3,4-epoxy-4-methyl-2-pentanone (8) photochemically isomerized to 3-methylpentane-2,4-dione (9). Zimmerman and coworkers[6] also noted an unexpected methyl migration when they found that 3,4-epoxy-4-phenyl-2-pentanone (10) rearranged photochemically to 1-phenyl-2-methyl-1,3-butanedione (11). They proposed the sequence shown in Scheme 1 to account for the β-diketone formation.

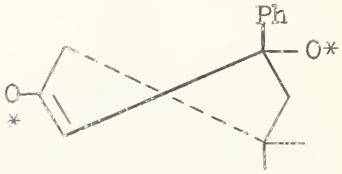
Scheme 1



The breaking of the C_α-O bond in 12 is analogous to the light-induced expulsion of electronegative groups attached to a carbon adjacent to an nπ*-excited carbonyl chromophore;[7] this reaction can be either a heterolytic or a homolytic process.

Because of the preferential methyl migration, which is analogous to the methyl-radical expulsion observed in the decompositions of cumyl peroxide[8] and phenyl-dimethylcarbinyl hypochlorite,[9] it was postulated that the C_α-O bond cleaved homolytically. Whether migration occurred by methyl-radical expulsion with intermolecular recombination, by migration with simultaneous electron demotion, or by intramolecular migration within the solvent cage was not known.

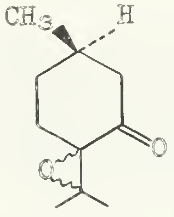
Phenyl migration might possibly be hindered by a steric effect; however, Reusch[5] noted that Drieding models show an easily accessible twist conformation (16) which can be formed in the isophorone oxide series, where no phenyl migration occurs.



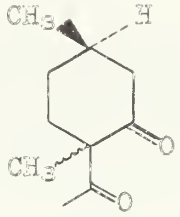
* = +,-,·

16

When the α-pulegone oxide 17 was irradiated it not only isomerized to the β-oxide 18, but also it rearranged to a mixture of the isomeric 2-acetyl-2,5-dimethylcyclohexanones 19 and 20.[5]



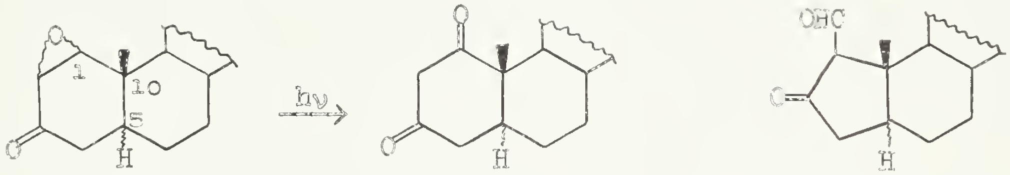
17, α-oxide
18, β-oxide



19, cis-methyl groups
20, trans-methyl groups

This isomerization implies that a reactive intermediate is reversibly formed, and this hypothesis is supported by the observation that the transition state for a concerted reaction must be contorted to obtain the necessary orbital overlap. Even though cleavage of the C_α-O epoxide bond accounts for the isomerization, homolytic fission of the C-C epoxide bond and rotation would also lead to the isomer 18.

Several photochemical rearrangements of α,β-epoxyketones to β-diketones in the steroid series have been studied. In the 1β,2-oxido-17α-acetoxyandrostan-3-one series (21,22) Wherli and his associates[10] found that a 1,2-hydrogen shift competed with a 1,10-bond migration to give a mixture of the β-diketone (23,24) and of the keto-aldehyde (25,26). The stereochemistry at the C_5 position was not affected. To explain these results it was postulated that carbonyl formation at C_1 and the competing hydrogen shift or bond migration were concerted.

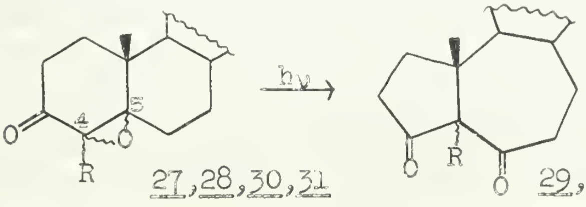


21, 5α
22, 5β

23, 5α
24, 5β

25, 5α
26, 5β

Jeger and coworkers[11] found that the 3-oxo-4,5-oxido steroids 27 and 28 gave the same β-diketone 29 regardless of the orientation of the oxirane ring. Unsaturation of the C_1-C_2 bond to produce an α,β-unsaturated ketone had no effect on the reaction.[12] When a methyl group was located at C_4 (30,31) the original stereochemistry was found in the respective products 32 and 33.[11] This stereospecificity was attributed to either a rigid cyclodecane system in the transition state or a 5-10 bond shift concerted with carbonyl formation at C_5.



27,28,30,31

29,32,33

27, R = H, α-epoxide
28, R = H, β-epoxide

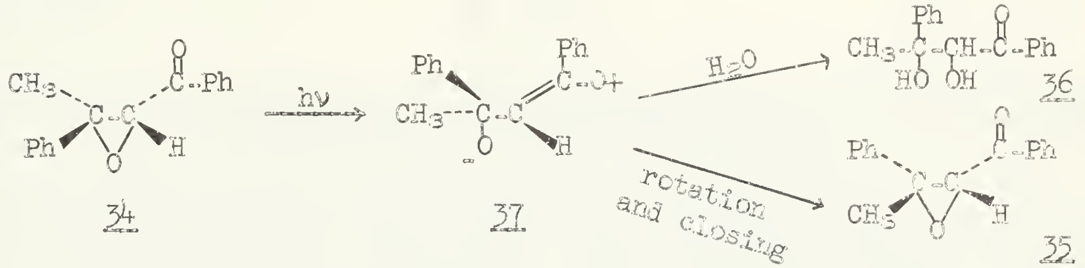
30, R = β-CH_3, α-epoxide
31, R = α-CH_3, β-epoxide

29, R = H

32, R = β-CH_3
33, R = α-CH_3

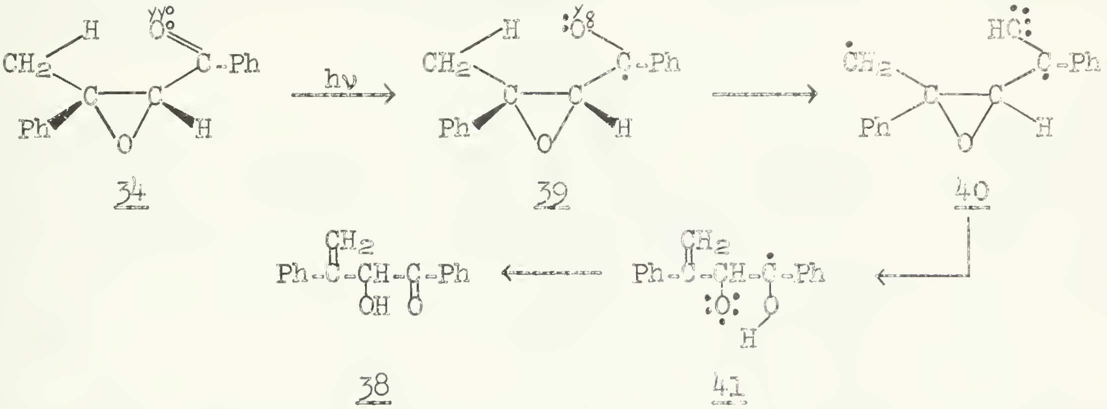
REACTIONS TO FORM KETO-ALCOHOLS

Zimmerman[13] noted that trans-dypnone oxide (34), when irradiated in aqueous ethanol, both isomerized to the cis-oxide 35 and reacted, probably with the water, to form the glycol 36 which reacted further to produce acetophenone and α-hydroxyacetophenone. He proposed that the zwitterion 37 was the intermediate from which both 35 and 36 arose.



Later Zimmerman and coworkers[6] reported that the photolysis of trans-dypnone oxide produced 1,3-diphenyl-3-buten-2-ol-1-one (38) in 25% yield; no solvent was mentioned. Cis-dypnone oxide (35), however, was inert when irradiated, indicating the necessity of the proximity of the methyl group. The sequence shown in Scheme 2 was proposed to explain the formation of 38.

Scheme 2



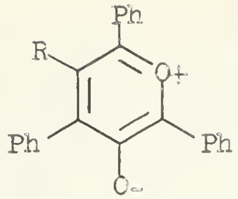
Hydrogen abstraction by nπ*-excited ketones is well known and is typified by the Norrish "Type II" elimination.[14] Padwa[15] has shown that the nπ* states of ketones resemble alkoxy radicals which are known to abstract protons. In species 40 the methylenic odd electron is conjugated with the strained oxirane ring which can open homolytically at the C_β-O bond. A simple intramolecular disproportionation of 41 can account for the observed products. It has been proposed that greater electron delocalization in the excited benzoyl group of 34 than in the excited acetyl groups of 8 or 10 leads to the difference in the photochemistry of these similar compounds. If the electron is localized on the carbonyl carbon atom it will be more available for breaking the C_α-O bond of the epoxide to form a β-diketone.[6]

CYCLOPENTENONE OXIDES

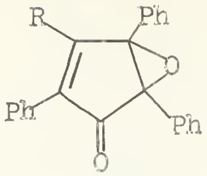
In a recent review of the photochemistry of pyrones, the reactions of the cyclopentenone oxides were reported.[16] The mechanisms of these reactions are discussed below.

Ullman and Milks[17,18] first reported the photochemical isomerization of the red 2,4,6-triphenylpyrylium-3-oxide (42) to the pale-yellow 4,5-epoxy-2,4,5-triphenyl-2-cyclopentenone (43) with visible light; irradiation of 43 with ultraviolet light instantaneously produced 42. In hydroxylic solvents 43 thermally rearranged to the 2-pyrone 44.

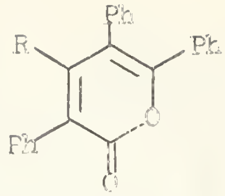
In 1937 Putter and Dilthey[19] observed that the 4,5-epoxy-2,3,4,5-tetraphenyl-2-cyclopentenone (45) produced tetraphenyl-2-pyrone (46) when exposed to sunlight; a transient pink coloration of the reacting solution was reported. Dunstan and Yates[20] later reported that when 45 was irradiated a new band rapidly formed in the



42, R = H
47, R = Ph



43, R = H
45, R = Ph

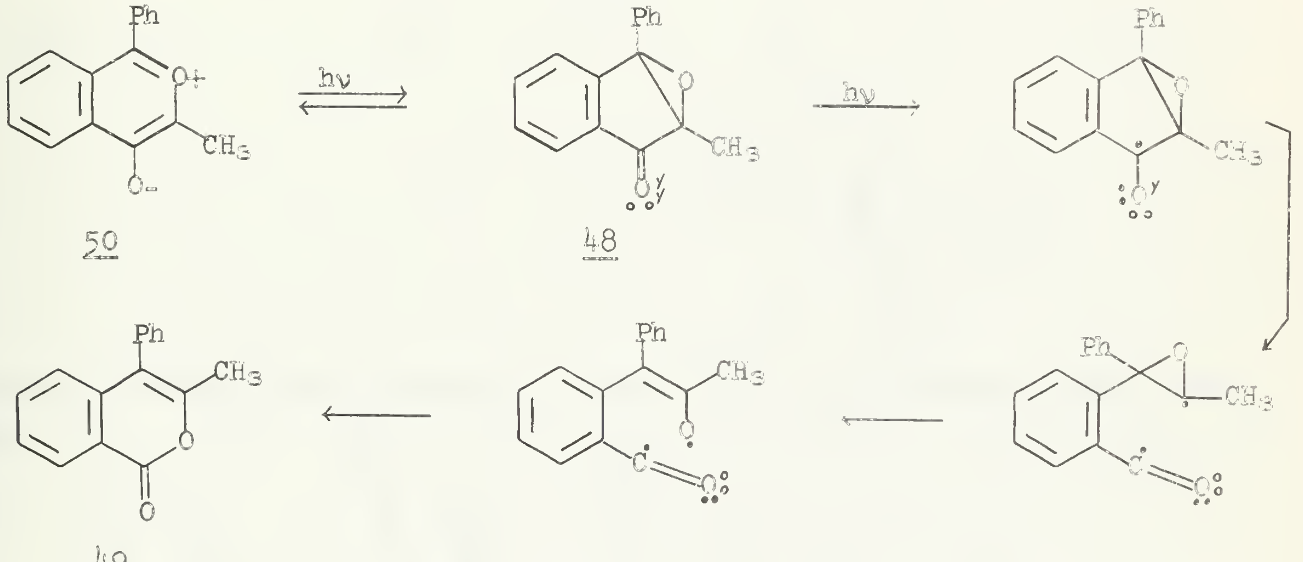


44, R = H
46, R = Ph

ultraviolet; slower formation of the 2-pyrone 46 also occurred. By isolating the perchlorate salt of the transient species they showed that it was the pyrylium oxide 47. It was claimed that experiments, which were not described, proved that the pyrylium oxide was not an intermediate in the pyrone formation.

Zimmerman and Simkin[21] reported that when 2,3-epoxy-2-methyl-3-phenyl-indanone (48) was irradiated an orange color formed in the reacting solution; it disappeared slowly as the isocoumarin 49 was produced. When dimethylacetylenedicarboxylate was included no color appeared, a new adduct was formed, and the yield of the isocoumarin was greatly reduced. Characterization of the adduct showed that the transient species was the pyrylium oxide 50. They proposed that the $n\pi^*$ state of the carbonyl was involved and postulated the sequence shown in Scheme 3 to account for the reaction. No experimental evidence for either including or excluding the pyrylium oxide 50 as an intermediate in pyrone formation was presented. They predicted that the carbonyl-to-C_2 bond was broken first; this cleavage is analogous to that in the Norrish "Type I" process.[22]

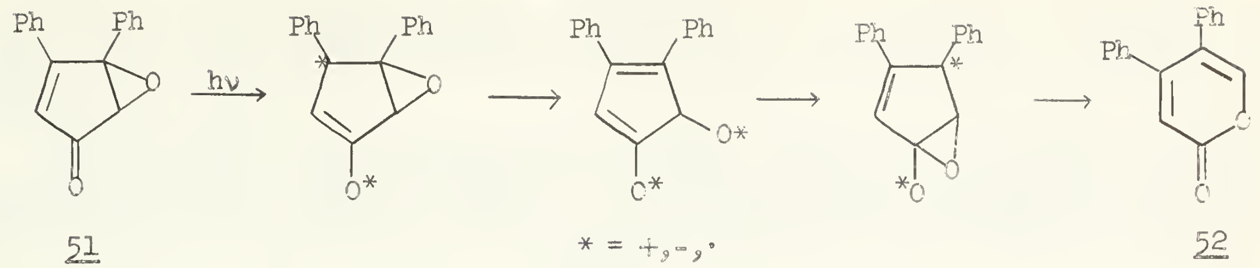
Scheme 3



Padwa and Hartman[23-25] found that 3,4-diphenyl-4,5-epoxy-2-cyclopenten-1-one (51) photochemically rearranged to the 2-pyrone 52 which further reacted to produce other products. No coloration was observed during the reaction, and attempts to isolate an intermediate pyrylium oxide were futile. No phosphorescence of the cyclopentenone oxide 51 was observed, and attempts to quench the photolysis with high concentrations of 1,3-pentadiene failed. These results indicate that the lowest triplet state of 51 probably did not participate in the reaction. It was not determined whether the $n\pi^*$ or the $\pi\pi^*$ singlet was involved. It has been suggested that the photochemistry of a molecule may be vastly different depending on which state is involved.[26] Since it is known that β-phenyl substituents affect the energy of $\pi\pi^*$ states,[27] the reactions of the different cyclopentenone oxides may be altered by their substitution patterns.[25] The sequence in Scheme 4 was proposed to explain the isomerization. It was postulated that the C_β-O bond of the oxirane ring was broken.

Ullman and coworkers,[28,29] in one of the most thorough studies of the photochemistry of an α,β-epoxyketone, reported that the 2,3-diphenylindenone oxide 53 underwent photochemically and thermally reversible isomerizations to the red pyrylium

Scheme 4



oxide 54. The deep-red solutions eventually reached a color intensity which depended on the relative rates of these thermal and photochemical isomerizations. Colorless solutions were slowly produced with continued irradiation.

When degassed benzene solutions of 53 were irradiated with ultraviolet light until a greatly reduced color intensity was obtained, and after the remaining pyrylium oxide 54 had been reconverted to 53 with visible light, 3,4-diphenylisocoumarin (55), the dimer 56, 3-phenylphthalide (57), and the indenone oxide 53 were isolated (runs 1-3, Table 1; Scheme 5).

Scheme 5

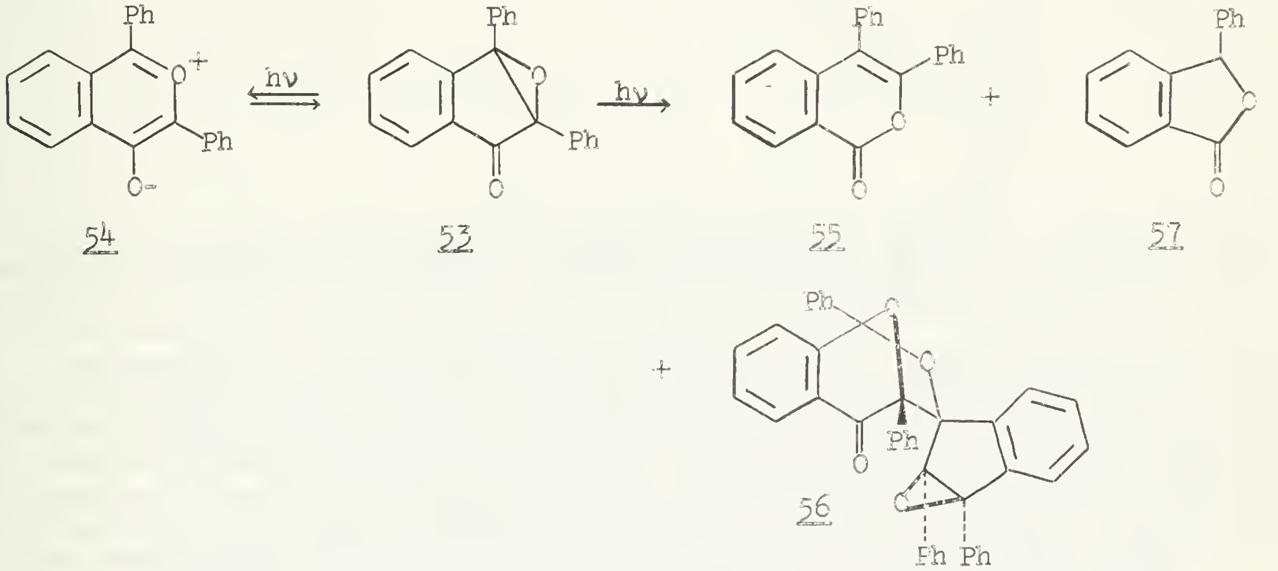


Table 1. Product Ratios Obtained on Irradiation of 2,3-Diphenylindenone Oxide

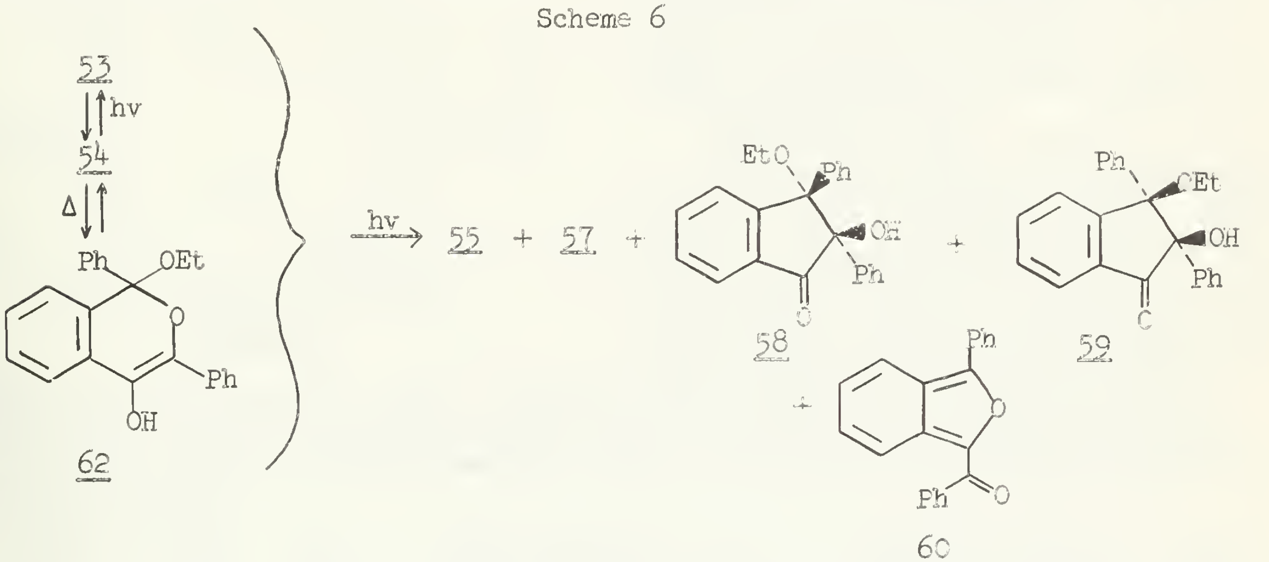
Run[a]	T °C	λ[b]	Time hr	Solv.	Conc. 10^{-2}M	53	55	56	57	58	59	60
1	25	UV	52	ØH	10.6	55		33				
2	25	UV	24	ØH	3.3	38	29	26	~5			
3	25	3650 A	36	ØH	3.3	39	26	23	~5			
4	145	VIS	102	ØH	0.5	100						
5	25	UV, VIS	24	ØH	0.9	39	53	<1	<1			
6	25	UV	36	EtOH	4.5	8	8			58	27	
{7	25	UV	11	EtOH	1.3	5	7			55	33	
8	25	UV, VIS	11	EtOH	1.3	14	33		T[c]	35	17	
9	125	VIS	22	EtOH	2.7	48	40		T[c]		10	T[c]
10	120	Dark	144	EtOH	2.7						76	11
{11	128	VIS	23	EtOH	1.6	29	47		T[c]		23	T[c]
12	128	Dark	23	EtOH	1.6		8					>64
{13	125	VIS	32	EtOH	1.6	15	57		T[c]		12	13
14	125	Dark	32	EtOH	1.6		6					88

[a] Bracketed runs were conducted simultaneously under identical conditions except for the different light sources. [b] Runs marked UV were irradiated with 3100-4000-Å light; those marked VIS were run with >4350-Å light. [c] T = trace.

When a benzene solution of 53 was heated and then irradiated with visible light only the indenone oxide 53 was recovered (run 4). Because the pyrylium oxide 54 was the dominant isomer at high temperatures, and because only it absorbed visible light, Ullman concluded that, in benzene, none of the products arose from the direct photolysis of 54.

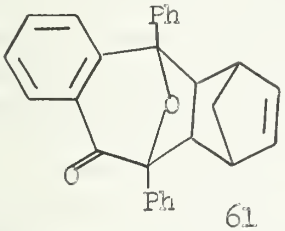
The red pyrylium oxide disappeared much more rapidly when ethanol solutions of 53 were irradiated. The two hydroxy ethers 58 and 59 and the isocoumarin 55 were the principal products (runs 6-7; Scheme 6). When only 54 was irradiated (run 9) the isocoumarin 55, the *cis*-hydroxy ether 59, the phthalide 57, and 1-benzoyl-3-phenylisobenzofuran (60) were isolated. Ullman reasoned that 58 was not formed photochemically from 54, and that the other products arose either photochemically from 54 or thermally.

Scheme 6



The isocoumarin 55 was formed in significant yields only when the pyrylium oxide 54 was irradiated; thermal reactions produced very little 55 (runs 11-14). Ullman therefore thought that 55 was formed either photochemically from 54 or thermally from 53. When any possible thermal reaction was eliminated (runs 7-8) visible light still produced an increased yield of 55. Ullman therefore concluded that, in ethanol, the isocoumarin was formed photochemically from 54; however, he did admit that these data do not conclusively preclude isocoumarin formation by the photolysis of 53.

Further control reactions showed that the formation of the *cis*-ether 59 and the isobenzofuran 60 was catalyzed by trace amounts of acid or base respectively. The *trans*-ether 58 was formed only with ultraviolet light, and the same was apparently true for the *cis*-ether (runs 6-8). The indenone oxide, however, was eliminated as a precursor when only trace amounts of 58 and 59 were found after irradiation of 53 with added norbornadiene, which quantitatively forms an unreactive adduct (61) with the pyrylium oxide 54. Ullman then experimentally confirmed that the hydroxy ethers, as well as the isobenzofuran, were formed from the enol 62 which is in thermal equilibrium with the pyrylium oxide 54.



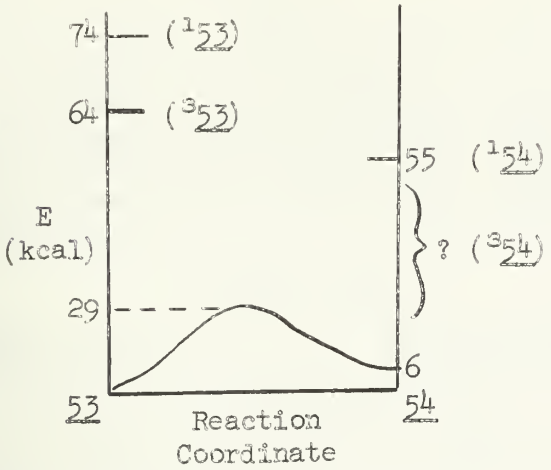
61

The conversion of the indenone oxide 53 to 54 in benzene could be partially quenched by naphthalene. A limiting quantum yield (ϕ_∞) of 0.49 was found with high concentrations of naphthalene. Because the quantum yield of the direct irradiation was 0.56, it was concluded that only 13% of the reaction involved the triplet of 53. Naphthalene did not quench the conversion in ethanol. Neither quenchers with low triplet energies nor di-*t*-butylnitroxide, which effectively quenches triplets,[30] affected the reverse reaction.

The conversion of 53 to 54 could be sensitized with benzophenone, and with high concentrations of benzophenone a quantum yield of 0.62 was measured. The effects of sensitizers with varying triplet energies (from 68.5 to 40 kcal) on the photostationary state (54/53) were studied. Sensitizers whose triplet energies were less than 64 kcal caused an abrupt change of the ratio (54/53) in the photostationary

state, indicating that non-vertical energy transfer did not occur. Because no further change occurred as the sensitizer energy was decreased, the triplet energy of 54 could only be defined as lower than that of its singlet state.

Fig. 1



All of the possible modes for the interconversion of the indenone oxide 53 and the pyrylium oxide 54 in their ground and lowest singlet and triplet states are summarized in equations 1-8. The endothermic, reverse reactions in 1-4 (see Fig. 1) are unlikely to occur. All of the forward reactions, which are exothermic, are considered below.

Experimental data exclude reaction 1, the conversion within the singlet manifold. If it occurred irradiation of the indenone oxide (to ^{1}53) would have produced immediate fluorescence from ^{1}54; however intense emission from ^{1}54 did not occur until the concentration of the pyrylium oxide had built up for several minutes. Product studies also preclude this route. Because both 53 and 55 are formed by direct irradiation of 54 (via ^{1}54), and because direct irradiation of 53 (via ^{1}53) gives only 54, ^{1}54 cannot be an intermediate in the conversion of the indenone oxide to the pyrylium oxide.

$$\begin{array}{llllll}
{}^1\underline{53} \rightleftharpoons {}^1\underline{54} & (1) & {}^3\underline{53} \rightleftharpoons {}^1\underline{54} & (4) & {}^1\underline{54} \longrightarrow \underline{53} & (7) \\
{}^3\underline{53} \rightleftharpoons {}^3\underline{54} & (2) & {}^1\underline{53} \longrightarrow \underline{54} & (5) & {}^3\underline{54} \longrightarrow \underline{53} & (8) \\
{}^1\underline{53} \rightleftharpoons {}^3\underline{54} & (3) & {}^3\underline{53} \longrightarrow \underline{54} & (6) & &
\end{array}$$

Measurements of the photostationary-state dependence on sensitizer energy indicate that non-vertical energy transfer does not occur in this system. If one accepts Ullman's proposal that the ability of a species to undergo non-vertical energy transfer is related to its tendency to undergo rapid exothermic rearrangement within the triplet manifold, then the conversion within the triplet manifold is probably not important (equation 2).

Because equation 3 involves a concerted change of both multiplicity and geometry it is a priori improbable. The data, however, do not exclude it.

Reaction 4 is also improbable because of the concerted multiplicity and geometry change; moreover, it is also precluded by the fluorescence data. Quenching studies showed that 13% of the conversion of 53 to 54 proceeded via ^{3}53. If ^{1}54 were formed from ^{3}53 fluorescence would be seen when only 53 is irradiated. Because fluorescence is observed only when 54 is irradiated, this route is not followed.

The only mechanisms which have not been eliminated are those which do not involve an electronically excited state of the product (eq 5-8). Ullman considered that in each of these processes an electronically excited state crosses over to a vibrationally excited ground state, which has the same energy and geometry as its electronically excited precursor at the instant of crossing. Rearrangement and collisional deactivation would then give the products.

Reactions of vibrationally excited states are known to occur in the gas phase, but their importance in solution has been discounted. Zimmerman and Wilson[31] have argued, using the Rice-Ramsperger-Kassel (RRK) theory,[32,33] that a unimolecular reaction cannot compete with collisional deactivation in solution. Ullman has re-examined the RRK theory for this isomerization.

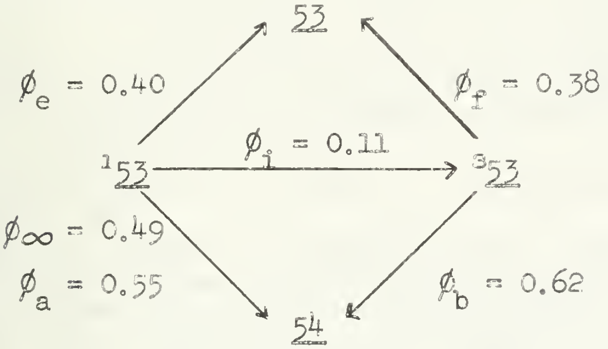
The RRK theory is given by equation 9 where $^*k$ is the rate of reaction of a vibrationally excited molecule having energy E, E_o is the activation energy of the thermal reaction, A is the frequency factor, and n is the number of vibrational degrees of freedom.

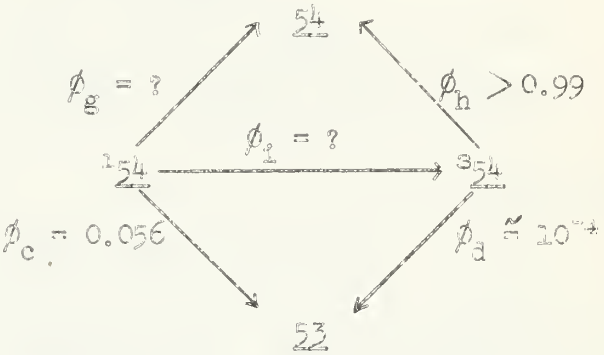
$$^*k = A\left(\frac{E - E_o}{E}\right)^{n-1} \qquad (9)$$

When reasonable values, taken from experimental data, were used with eq 9 a value

of $n = 9.2$— a value far too low for the indenone oxide— was calculated. Ullman therefore suggested modification of the RRK theory.

Implicit in the RRK theory is the assumption that the vibrationally excited species is produced with a random distribution of vibrational energy, and that the rate of reaction depends on the probability of this energy being concentrated at the reaction site; therefore, as the number of atoms is increased the rate of reaction should decrease. When the vibrationally excited state is formed by crossing from an electronically excited species, however, the energy distribution is governed by the restrictions of the Franck-Condon principle. Ullman therefore postulated that the energy needed for reaction might already be concentrated at the reaction site in the vibrationally excited molecule. If this energy were originally concentrated, *k would also depend on the rate of energy randomization in the molecule. These concepts are tested below.





These data show that, if vibrationally excited, ground-state molecules are derived from ^{1}53 and ^{3}53 before 54 is formed, then the probabilities of forming 54 from the vibrationally excited species of either ^{1}53 or ^{3}53 are strikingly similar ($\phi_a \sim \phi_b$). Because the quantum yields ϕ_a and ϕ_b have slightly different values, Ullman postulated that two vibrationally excited species differing slightly in energy distribution may be formed from ^{1}53 and ^{3}53.

It can be seen that the probability of forming the indenone oxide 53 from a vibrationally excited species derived from ^{1}54 is much greater than from one formed by crossing from ^{3}54 ($\phi_c >> \phi_d$). Because the energy of ^{3}54 might be near that of the activation barrier of the thermal reaction (Fig. 1), this result is not unreasonable. The temperature dependence of the quantum yields of the conversion of 54 to 53 also supports this view.

Many aromatic ketones undergo intersystem crossing with quantum yields near unity;[34] however, the data show that the efficiency of internal conversion to the ground state of ^{1}53 (ϕ_e) is almost four times that of intersystem crossing (ϕ_i). The short lifetime of ^{3}53 (5×10^{-9} sec) indicates that it undergoes an enhanced intersystem crossing (ϕ_f). Fast reactions of the electronically excited states do not seem reasonable because about 40% of the molecules that undergo crossing from either of these excited states are unchanged; therefore, Ullman reasoned that the photochemical reactions of the indenone oxide are related to its increased rates of crossing from its electronically excited states.

Calvert and Pitts[35] have criticized Ullman's interpretation of these results. They propose that ^{1}53 goes to ^{3}54 in the direct irradiation (eq 3), and that ^{3}53 forms ^{1}54 in the sensitized rearrangement (eq 4). Ullman's criticisms of these processes have already been discussed. They also suggest that an intermediate structurally distinct from both 53 and 54 occurs in the reverse reaction, but they do not tell what they think it might be. No evidence of an intermediate in the conversion of 54 to 53 has been found, but this result certainly does not preclude one.

Quantum yields exhibit a marked wavelength dependence when vibrationally excited species are involved. If such a dependence were found it would certainly substantiate Ullman's proposal. Great experimental care would be needed to avoid a confusing intensity effect.

In the cyclopentenone-oxide series the quantum yields decrease as smaller substituents are attached to the oxirane ring. In contrast to Padwa's proposal (*vide supra*) Ullman proposes that this effect is caused by the diminished ability of

the lighter groups to prevent randomization of the energy of a vibrationally excited, ground-state intermediate. Obviously more experimental work is needed to elucidate the mechanisms of the photochemical reactions of the cyclopentenone oxides.

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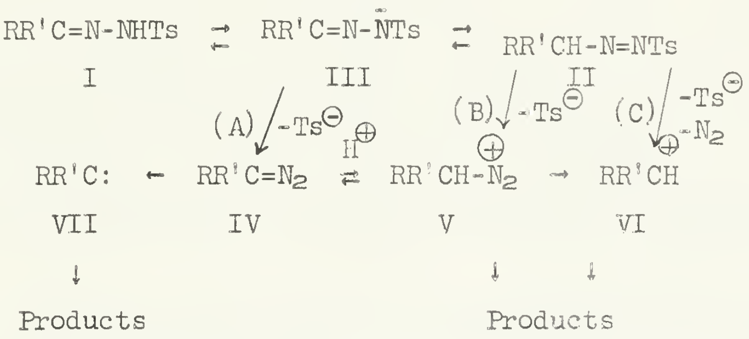
THE BAMFORD-STEVENS REACTION

Reported by Peter A. Gebauer December 7, 1967

INTRODUCTION

The Bamford-Stevens[1] reaction of p-toluenesulfonylhydrazones (tosylhydrazones) with base to form olefins or products arising, at least formally, from carbene insertions is generally considered to proceed via a cationic or carbenic mechanism, depending on the proton donating ability of the solvent (Scheme 1). It has also been suggested that a carbanionic mechanism is operative under certain conditions.[2,3]

Scheme 1



The purpose of this seminar will be to present the evidence for these mechanisms and also to present the recent work related to the Bamford-Stevens reaction in the cyclobutane, cyclopropylcarbinyl and other ring systems.

THE "CARBENE" AND "CARBONIUM ION" MECHANISM

Bamford and Stevens[1] found that reacting the tosylhydrazones of aliphatic ketones with sodium in ethylene glycol yielded olefins while the presence of a phenyl group next to the tosylhydrazone group generally resulted in the formation of azines or dimers of the corresponding carbenes. Under mild conditions, diazo compounds could be isolated. Camphor tosylhydrazone formed optically active camphene as the only product. Since Heubaum and Noyes[4] had found that diazocamphane yielded only tricyclene, Bamford and Stevens felt that the diazo compound was not always formed and that the anion of the tosylhydrazone might decompose directly to products.

Later work by Powell and Whiting[5] indicated, however, that some tricyclene actually was formed under the conditions employed by Bamford and Stevens.

Other early proposals for the mechanism of this reaction often involved the tautomer of the tosylhydrazone (II). Corey and Sneen[6] suggested that the tosyl group abstracted an α-hydrogen as the tautomer decomposed concertedly to olefin, nitrogen, and p-toluenesulfinic acid. DePuy and Froemsdorf[7] suggested that toluenesulfinate anion and nitrogen were lost from II to form a carbonium ion which lost a proton to form olefin (Path C). They also considered the possibility that an intermediate diazonium ion (V), analogous to those presumed[8] to be formed in the deamination of amines (Eq. 1) and in the decomposition of N-nitroso-N-alkylamides (Eq. 2),[9] might be formed (Path B), but ruled this out on the grounds that deamination reactions generally produce greater proportions of trans olefins than are found in the Bamford-Stevens reaction.

Eq. 1 $$R\text{-}NH_2 \rightarrow R\text{-}N{=}N\text{-}OH \rightarrow R\text{-}N_2^{\oplus} + OH^{\ominus}$$

Eq. 2 $$R\text{-}\overset{NO}{N}\text{-}CO\text{-}R' \rightarrow R\text{-}N{=}N\text{-}O_2CR' \rightarrow R\text{-}N_2^{\oplus} + O_2^{\ominus}C\text{-}R'$$

However, the intermediacy of II in the Bamford-Stevens reaction seems unlikely since there would be apparently no need for the strong base which is required in this reaction. It has been found[10] that carbonate is not sufficient to cause the decomposition even though it would certainly be basic enough to abstract a proton from the diazonium ion or other cationic species.

It is now generally accepted that the Bamford-Stevens reaction proceeds via the corresponding diazo compound (Path A). Direct evidence for this has been: 1) the isolation of diazo compounds under conditions very similar to those of the Bamford-

Stevens reaction[1,13-16] and 2) the formation of products which, under other conditions, are known to arise from diazo compounds[1,17] or from carbenes.[18] It should be pointed out, however, that in most of these cases, the diazo compound is a phenyl- or a diphenyldiazomethane which is much more stable than other alkyldiazomethanes and so it could be that diazo compounds are intermediates only under these circumstances.

Indirect evidence for the intermediacy of diazo compounds has been the formation of products which arise, at least formally, from carbene insertions into carbon-hydrogen bonds.[5,19] However, recent work has indicated that insertion products can also arise partially, and in some cases mainly, from cationic intermediates.[20-22]

Although the loss of toluenesulfinate from the tautomer of the tosylhydrazone seems unlikely, Powell and Whiting[5] suggested that protonation of the diazo compound to form an intermediate diazonium ion in hydroxylic solvents might be invoked in order to explain the variation in the product composition from the decomposition of camphor tosylhydrazone in various solvents. Although tricyclene and camphene were the only C_{10} hydrocarbons which were obtained, the relative yield of tricyclene varied from 12% in glycerol to better than 97% in acetamide.

Friedman and Shechter[23] also found that the tricyclene:camphene product ratio varied with solvent and noted that in the decomposition of other tosylhydrazones the ratio of unrearranged olefins to rearranged olefins was greater in less protic solvents.

Both of these groups concluded that an intermediate diazo compound was decomposing thermally in aprotic solvents while in protic solvents an acid catalysed, "cationoid" pathway also was operative.

Labeling studies, carried out in deuterated hydroxylic solvents, are consistent with this mechanism since the products which are favored in protic solvents also incorporate nearly one mole of deuterium per mole of product.[10,24,25] The fact that less than the theoretical amount of deuterium is incorporated has been explained by assuming that a deuterium isotope effect is operative.[10,25] The deuterium isotope effect has also been invoked to explain the decrease in the relative yield of the products which are favored by protic solvents when the reaction is run in deuterated solvents.[24] Both of these observations are consistent with the proposed mechanism.

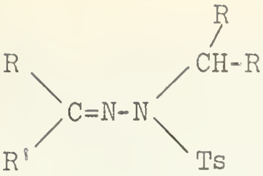
However, it has also been found that the products disfavored in protic solvents are also formed with incorporation of deuterium when the reaction is run in deuterated solvents,[10] which is inconsistent with this mechanism.

The formation of ethers, presumably through nucleophilic attack of solvent on an intermediate cation, has also been used as evidence for a cationic intermediate. Ethers were isolated by Powell and Whiting[5,26] but not by Friedman and Shechter.[23] However, the latter workers noted that the yields were lower in protic than in aprotic solvents and the formation of ethers as side products might account for this

Since diazo compounds vary in their sensitivity to acids,[27] it is quite hard to make a definite distinction between "protic" and "aprotic" solvents. For instance, Kirmse[28] has pointed out that although Powell and Whiting[5] concluded that acetamide was an aprotic solvent in the decomposition of camphor tosylhydrazone, it appears to be protic in the decomposition of pivaldehyde tosylhydrazone, since a large amount of rearranged olefin is formed.[29] However, Friedman and Shechter[23] have pointed out that in reactions in which alkoxides are used as bases, the protonation of the diazo compound is not completely suppressed even in very aprotic solvents since an equivalent of alcohol is formed when the base reacts with the tosylhydrazone. Since the work with camphor tosylhydrazone was carried out using sodium in acetamide as the base while sodium methoxide was the base in the pivaldehyde tosylhydrazone decomposition, it would seem likely that the difference in mechanism is due to protonation of pivaldehyde tosylhydrazone by methanol which is not present in the work with camphor tosylhydrazone.

Shapiro, Duncan and Clopton[10] have found that the proportion of product formed by a cationic pathway increased with the polarity of the solvent even though all the solvents which were used were aprotic. They attribute this to greater protonation of the diazo compound by methanol in the more polar solvent

Another possible proton source in the reaction is the tosylhydrazone itself. Dornow and Bartsch[17] found products such as VIII when aryltosylhydrazones were treated with less than one equivalent of base. Analogous products were found in

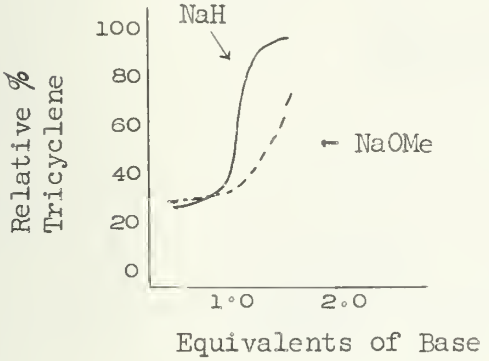


VIII

the reaction of diazomethane and diphenyldiazomethane with tosylhydrazones and presumably all of the reactions occur through protonation of the diazo compound by unreacted tosylhydrazone.

Shapiro and co-workers[10] have studied the effect of the amount of base on the product distribution, and the results using sodium methoxide and sodium hydride as the base in dimethylformamide are shown in Figure I. In less polar solvents the shape of the curve was approximately the same, but camphene was less strongly favored with less than one equivalent of base and there was a smaller difference between the results with sodium methoxide and with sodium hydride at higher base concentrations.

Figure I. Relative Yield of Tricyclene Using Varying Amounts of Sodium Methoxide and Sodium Hydride in DMF



With less than one equivalent of base, the results are nearly the same whether sodium methoxide or sodium or sodium hydride is used as the base, which would tend to indicate that unreacted tosylhydrazone, rather than methanol, was the proton source. With more than one equivalent of base, the tosylhydrazone is probably entirely in the form of the anion,[5] and methanol is the proton source, which would account for the discrepancy between the results using sodium methoxide and sodium hydride under these conditions.

Shapiro and co-workers also found that when the reaction was run in diglyme containing deuterium oxide, as much as 65% of the tricyclene contained incorporated deuterium, depending on the amount of base present. From their data, they concluded that the anion of the tosylhydrazone was decomposing to form the diazo compound which was in equilibrium with the diazonium ion (see Scheme I). The diazo compound was expected to decompose, via a carbene, to tricyclene while the diazonium ion could decompose, either concertedly or via a carbonium ion, to either camphene or tricyclene.

The critical step in this mechanism is the equilibrium between the diazo compound and the diazonium ion.[10] More O'Ferrall[8] has discussed the reversibility of the proton transfer to diazo compounds and has concluded that it depends mainly on the stabilities of the diazo compound and the cation resulting from the decomposition of the diazonium ion. For instance, diphenyldiazomethane reacts with acids in a rate determining, irreversible protonation while loss of nitrogen is the rate determining step in the acid catalysed decomposition of ethyldiazoacetate and the protonation is reversible.[8] These conclusions are based on the facts that the diphenyldiazomethane decomposition is first order in both acid and diazo compound and has a deuterium isotope effect of $k_H/k_D = 3.3$[11] and that the exchange of α-hydrogens in ethyldiazoacetate is faster than the overall hydrolysis.[8] Kirmse and Rinkler[30] found that 1-diazobutane decomposes in methanol-d_1 to form 1-methoxybutane-d_1. They concluded that the protonation must be the rate determining step since no dideuterated material was obtained. It would seem from this limited amount of data that the reversibility of the protonation of the diazo compound in the Bamford-Stevens reaction is greatly dependent on the system involved and that no general conclusion can be drawn concerning the reversibility of this step.

If the postulated mechanisms are correct, the aprotic Bamford-Stevens reaction should yield products similar to those found in the oxidation of hydrazones and other processes in which a diazo compound is presumed to be formed, while the protic Bamford-Stevens reaction should be similar to the deamination of amines and other cationic processes.

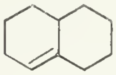
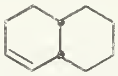
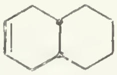
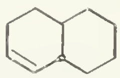
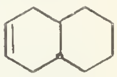
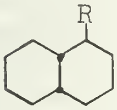
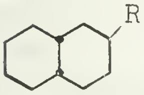
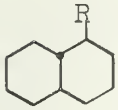
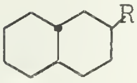
Reusch, Whiting and co-workers[31] have studied the effect of solvent on the product distribution from the oxidation of camphor hydrazone and found that there

was a solvent effect similar to that found in the decomposition of camphor tosylhydrazone. Powell and Whiting[5] found that the tricyclene:camphene ratio from the decomposition of N-nitroso-N-carbethoxybornylamine in 2-ethoxyethanol approached that found in the decomposition of camphor tosylhydrazone in the same solvent.

Hückel and Nerdel[32] found that the deamination of bornyl- and isobornylamines yielded camphene and camphene hydrate, along with other products, but no tricyclene was formed, while Heubaum and Noyes[4] found that diazocamphane yielded only tricyclene. It is attractive to postulate that the Bamford-Stevens reaction is a competition between two processes analogous to those just mentioned, but labeling studies have led Nickon and Werstiuk[22] and Shapiro and co-workers[10] to conclude that tricyclene is also formed by a cationic pathway. It would thus seem likely that the cationic intermediate proposed for the protic Bamford-Stevens reaction is different from the intermediate in the deamination reaction.

The results in the Bamford-Stevens reaction in the decalin series[26] are shown in Table 1 along with the results of the deamination of the corresponding amines.[33]

Table 1. Comparison of Deamination and Bamford-Stevens Reaction in Decalin Series

Decalin[a]	Reaction	Relative Yield %				
						
	Acetamide[b] Glycol[c] Amine[d]	25 27 12	75 73 88			
	Acetamide Glycol Amine		51 48 30	49 52 70		
	Acetamide Glycol Amine	74 82 50			26 18 50	
	Acetamide Glycol Amine				35 45 30	65 55 70

a. R indicates position of amino or tosylhydrazone group
b. Tosylhydrazone in sodium and acetamide[26]
c. Tosylhydrazone in sodium and ethyleneglycol[26]
d. Axial amine deamination, equatorial amine yields exclusively alcohols[33]

Powell and Whiting[26] assumed that the reaction of the tosylhydrazones in acetamide proceeded without protonation of the diazo compound, and stated that the relative yields of olefins could be rationalized on the basis of the formation of a carbene and hydrogen migration to form a statistical mixture of olefins which slightly favored the more stable isomer. They suggested that in ethylene glycol diazonium ions were formed. They expected the equatorial diazonium ions to yield mainly substitution products[33] while the axial diazonium ion was expected to undergo 1:2 elimination to form olefins in approximately the same ratio as the carbene. However, the deamination of the axial amines[33] does not justify the latter conclusion. It would seem that either the cationic intermediates in the processes are not the same, or the olefins arise nearly exclusively from the carbene while protonation of the diazo compound forms only equatorial diazonium ions which lead to substitution products.

Bayless and co-workers[34] have compared the protic decomposition of cyclopropanecarboxaldehyde tosylhydrazone to the protic and aprotic deamination of cyclopropylcarbinyl amine and to the deoxidation of cyclopropylcarbinol. They concluded that the difference in the products was determined by the energy contents of the intermediate cations.

RATE DETERMINING AND PRODUCT DETERMINING STEPS

Powell and Whiting[5] studied the kinetics of the Bamford-Stevens reaction by following the evolution of nitrogen and found that: 1) the reaction was first-order in tosylhydrazone; 2) there was no change when the base concentration was decreased but still kept at greater than one equivalent; 3) methanesulfonyl and p-toluenesulfonyl hydrazones reacted at different rates; 4) camphor tosylhydrazone and cyclohexanone tosylhydrazone reacted at the same rate; and 5) the reaction was faster in less polar solvents. They concluded that the rate determining step was the loss of toluenesulfinate anion before any skeletal rearrangement had occurred. Since diazo compounds had been isolated in this reaction they felt that a diazo compound was formed in this step. However, it should be noted that the isolation of diazo compounds also indicates that the loss of toluenesulfinate cannot be the rate determining step in all cases. The solvent effect on the rate was the reverse of what they expected but they felt that the formation of complexes due to hydrogen bonding probably made predictions concerning this point difficult.

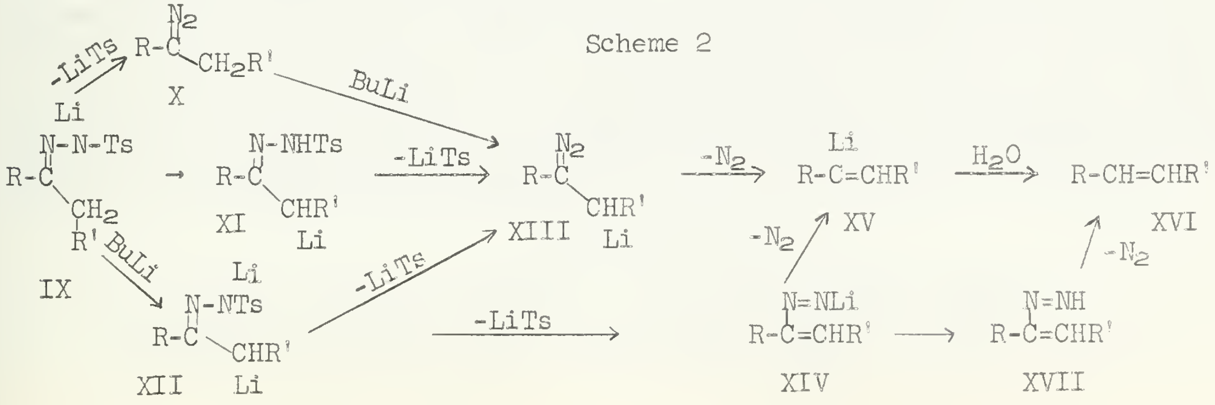
DePuy and Froemsdorf[7] found that the olefins were formed in the Bamford-Stevens reaction following Saytzeff's Rule and that the trans:cis ratio was close to one and concluded that the process was an E_1 elimination. However, the product distribution is determined by the molecularity of the product determining step which may not necessarily be the rate determining step. Thus, even though the decomposition of the anion may be the rate determining step, and is indeed a unimolecular decomposition, the product distribution cannot be used as an argument for a unimolecular rate determining step since the product composition is undoubtedly determined at some later stage in the mechanism.

THE CARBANION MECHANISM

Kirmse and co-workers[2] found that the decomposition of tosylhydrazones with sodium hydride or sodamide in decalin yielded a much larger proportion of unrearranged product than sodium methoxide in diglyme. Shapiro and Heath[35] and Shecter and co-workers[36] found similar results using alkyl lithiums as the bases. All of these workers concluded that a carbanionic mechanism, presumably initiated by the abstraction of an α-hydrogen from the tosylhydrazone or its anion, was operative in these cases. In support of this it was found that pivaldehyde did not react under the carbanion conditions but did react with sodium methoxide,[2] that α,β-unsaturated tosylhydrazones yielded dienes[2] rather than cyclopropenes,[18] and that a proton from some source other than the starting material is placed on the carbon previously bearing the tosylhydrazone group.[2,36,37] Shecter and co-workers also found that deuterium was incorporated when salts of tosylhydrazones were warmed in ethylene glycol-d_2.[36]

Although it appears certain that α-hydrogen abstraction does occur, the other steps in the mechanism are still in doubt. Various workers have proposed the following possible mechanisms.[3,34,37]

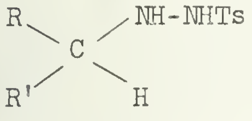
Scheme 2



Shapiro[35] has studied the stereochemical results of the decomposition of tosylhydrazones of various phenyl ketones (IX, $R=\phi$, ϕCH_2, $R'=\phi$, ϕCH_2, CH_3) and concluded that the carbanionic decomposition of these compounds yielded more cis olefin than the carbenic decomposition or the acid catalysed dehydration of the corresponding alcohols. For instance, when IX ($R=\phi$, $R'=CH_3$) was treated with methyl lithium in ether, presumably a carbanionic process, the cis:trans ratio in the products was 76:24 while using sodium methoxide in diglyme as an example of a carbenic decomposition gave a cis:trans ratio of 20:80. The acid catalysed dehydration of alcohols, as an example of a carbonium ion process, had a cis:trans ratio of 5:95. He argued that the intermediate carbene and carbonium ion were equilibrating to the trans isomer which he assumed was preferred. He felt that the carbanion or lithium derivative also should have equilibrated under the reaction conditions and therefore ruled these out as possible intermediates since he felt that the trans isomer would have been preferred in this equilibrium also. No quantitative data are available concerning the position of the equilibrium between the cis and trans vinyl lithiums which were studied, and so conclusions based on assumptions concerning this equilibrium are quite tenuous.

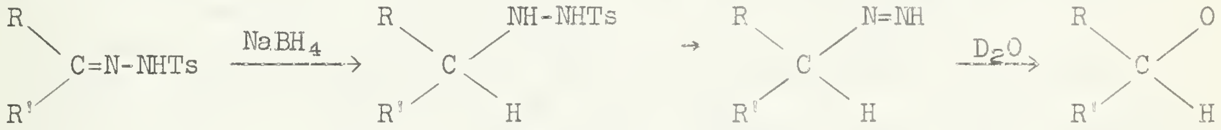
At the moment, there appears to be no compelling evidence for the choice of any one of the possible mechanisms over the others. They all account for the loss of an α-hydrogen and the incorporation of a hydrogen from the quenching material, but none seem to offer an obvious explanation for the stereochemical results.

Cagliotti and co-workers[38] have found that tosylhydrazones react with lithium aluminum hydride or sodium borohydride to form methylene groups or to form olefins, presumably by the mechanism just discussed. Since tosylhydrazides (XVIII) are known[39] to decompose with or without base catalysis to methylene groups and since tosylhydrazides have been isolated in the reaction of tosylhydrazones with lithium aluminum hydride, it has been proposed that the reduction proceeds via these compounds.[38]



XVIII

Further evidence for the intermediacy of tosylhydrazides was presented by Djerassi and co-workers[37] who found that one of the methylene protons replacing the tosylhydrazone group came from the hydride while the other came from the water which was used to quench the reaction. These results were consistent with the following scheme.



Olefins were formed in cases in which the carbon-nitrogen bond was sterically protected from attack by the hydride[37] and so it seems that the course of the reaction of tosylhydrazones with metal hydrides is probably determined by steric effects. If the carbon-nitrogen bond can be attacked, reduction occurs while if this process is sterically hindered, olefins will be formed by a carbanionic mechanism.

CONCLUSION

It seems certain that the Bamford-Stevens reaction can proceed by at least three mechanisms. Which mechanism predominates depends on the polarity and proton donating ability of the solvent, the amount and the type of base used, and probably, at least to some extent, the structure of the tosylhydrazone. It would seem, however, that more work is needed to determine exactly which mechanism is operative under which conditions and, particularly, to determine the form of the intermediate in the "cationic" decomposition and its relationship to the presumed diazonium ion intermediate in the deamination of amines.

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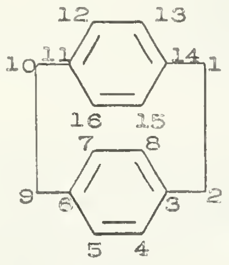
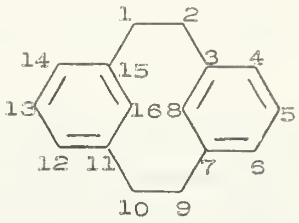
STRUCTURE AND REACTIVITY OF [2.2]PARACYCLOPHANES AND [2.2]METACYCLOPHANES

Reported by Doug McCullough December 11, 1967

Paracyclophanes and metacyclophanes have been the concern of much recent research in organic chemistry.[1,2] Probably [2.2]paracyclophane (I) and [2.2]metacyclophane (II) are the most interesting compounds in the respective series. This seminar will examine literature concerning the latter two compounds and their derivatives from a structural viewpoint, correlating their unique characteristics with reactivity.



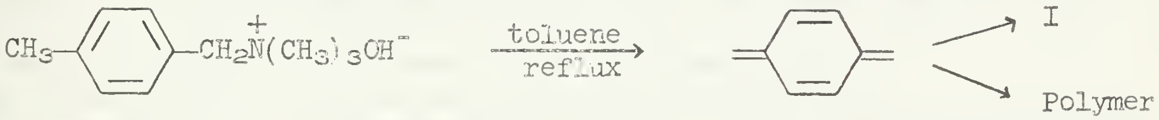
I



II

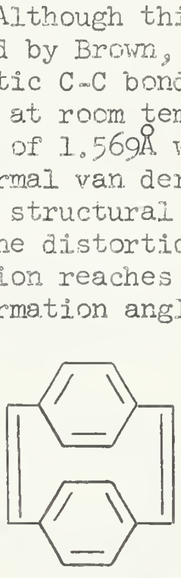
[2.2]PARACYCLOPHANE

This compound is usually synthesized[3] by 1,6 Hoffmann-type elimination of p-methylbenzyltrimethylammonium hydroxide (III). The intermediate, p-xylylene (IV), gives the desired product (I) in about 17% yield. Syntheses of derivatives of I as well as many other cyclophanes have been discussed in detail recently.[4]



III IV

The crystal structure of [2.2]paracyclophane was determined by Brown in 1953.[5] The crystal is tetragonal and contains two molecules with mmm symmetry per unit cell. Brown obtained a crystallographic R-factor of 0.14. In an independent study, Lonsdale, Milledge, and Rao determined the structure at 291°K and 93°K with the interest of studying thermal expansion and molecular vibrations.[6] The structure was refined to an R-factor of 0.105 in this work. Although this structure has the same 3.09Å maximum inter-ring distance that was reported by Brown, it differs in other respects. Bekoe and Trueblood[7] noted that the aliphatic C-C bond in the bridge was unusually long in the Lonsdale structure, being 1.630Å at room temperature. In a re-investigation of the structure, they obtained a value of 1.569Å with an estimated standard deviation of 0.008Å for the bridge bond. A normal van der Waals distance between two benzenoid rings is of the order of 3.4A.[6] The structural results from these researches demonstrated the significant out-of-plane distortion in the benzenoid rings arising from their close proximity. Ring distortion reaches a maximum in V, the diolefin of [2.2]-paracyclophane.[8] The pertinent deformation angles for these structures are indicated

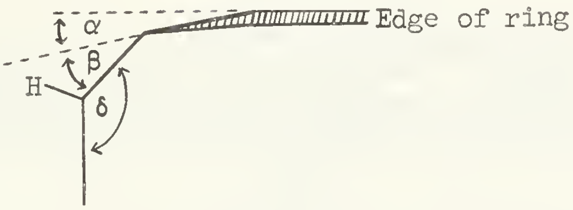


V

in the following diagram.[9]

Some Deformation Angles in the [2.2]Paracyclophanes

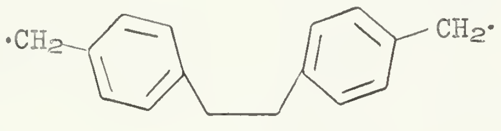
		α	β	δ
[2.2]Paracyclophane	(a) Brown, 1953	11	14	115
	(b) Lonsdale *et al.*, 1960	14	7	111
	(c) Bekoe and Trueblood, 1964	13	10	113
Diolefin of [2.2]-Paracyclophane		14	15	119



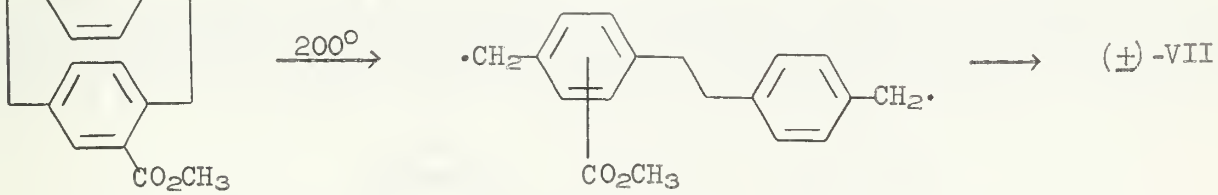
Unusual spectral effects have been observed for I and its derivatives.[10,11] In the ultraviolet they are usually interpreted in terms of both transannular π electron interactions between the two rings, and distortion of the aromatic rings from their normal planar configurations.[10] The n.m.r. spectra of 2.2 paracyclophanes exhibit shifts of the centers of gravity of the aromatic protons to higher field than the corresponding open-chain model compounds.[1,12] Aryl protons of I give a peak at 3.63τ which can be compared to the usually accepted range of 2.0 to 3.5τ.[1] Possible reasons for this shift include disruption of ring currents due to the highly puckered state of the rings,[13] a slight rehybridization toward sp^3, and transannular shielding effects.[1,14]

A consequence of the highly deformed structure of I is an appreciable strain energy. Boyd[15] found a strain energy of 31 k.cal./mole based on calorimetric measurements. Both Trueblood[9] and Boyd felt that the largest contribution to strain is from the out-of-plane deformation of the benzene rings. Release of this strain energy has been effected in a number of ring opening reactions.

The paracyclophane ring has been opened photochemically by both heterolytic and homolytic cleavage of the bridge methylene bonds.[10] Evidence has been presented which demonstrates that thermal cleavage of [2.2]paracyclophanes at 200° leads to the *p*,*p*'-dimethylenebibenzyl diradical (VI), the fate of which depends on the medium. In their experiments Reiche and Cram[16] heated (-)-4-carbomethoxy[2.2]paracyclophane (VII) in both dimethyl sulfone and *n*-tridecane for 13.3 hours at 200°. In the former solvent recovered VII was found to be 13% optically pure, while in the latter solvent the value was 5.6%. The amount of recovered VII in both reactions was 83%. Their data gave a ratio of one-point first-order rate constants of 0.7 for k_{DS}/k_{TD}. The proximity of the two aromatic rings makes ring opening the only path by which racemization can occur. Diradical VIII along with xylylenes IV and IX were considered as possible intermediates by the authors. The apparent insensitivity of the rate to solvent

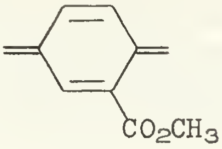


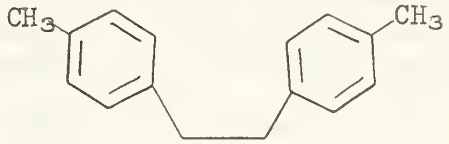
VI



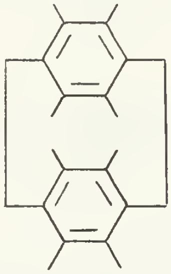
(-)-VII VIII

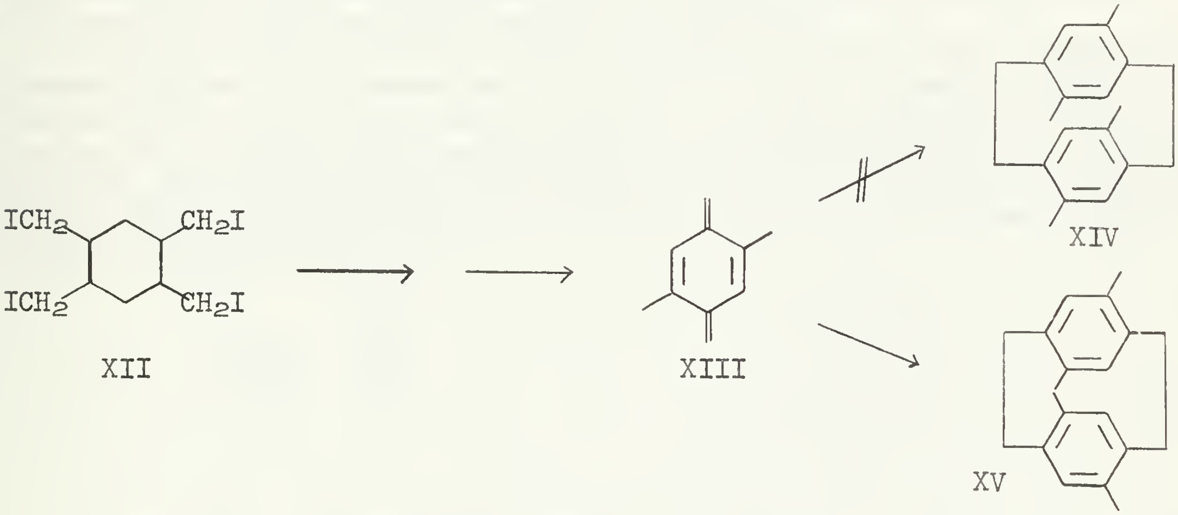
polarity made a zwitterionic species unlikely. That the diradical VIII is an intermediate was further indicated when X was produced in 21% yield by heating I at 250° in p-diisopropylbenzene.[16]


IX

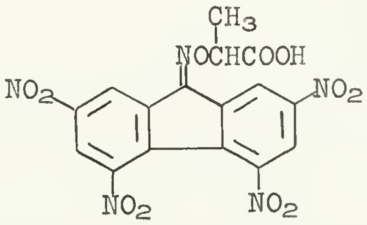

X

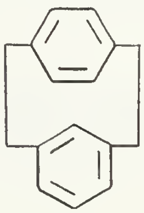
Thermal ring opening of I at 400° gave p,p'-dimethylbibenzyl and p,p'-dimethylstilbene,[17] while pyrolysis at 600° gives xylylene.[18] Similar behavior is noticed with various aryl-substituted [2.2]paracyclophanes at 550-600°.[19] It is noteworthy that octamethyl [2.2]paracyclophane (XI) decomposes in solution at room temperature or in the solid state to give insoluble polymer.[20] This represents an extreme case of eclipsing of alkyl groups. In the dehydroiodination of XII Longone and Warren considered XV to be the preferred product because of transannular eclipsing of the methyl groups in XIV.[21] That the structure is XV has been demonstrated recently by partial resolution using optically active XVI as a complexing reagent.[22]


XI



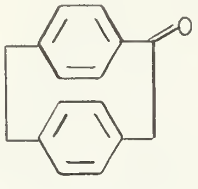
Some ring opening of I was observed by Cram and Fischer in acylation experiments under Friedel-Crafts conditions.[23] In other work by Cram and co-workers, I was treated with aluminum chloride and hydrogen chloride in methylene chloride solution at 0°.[24] Among the products isolated and purified was the desired crystalline material XVII in 44% yield. The authors thought that I and XVII might have similar amounts of ring


XVI


XVII

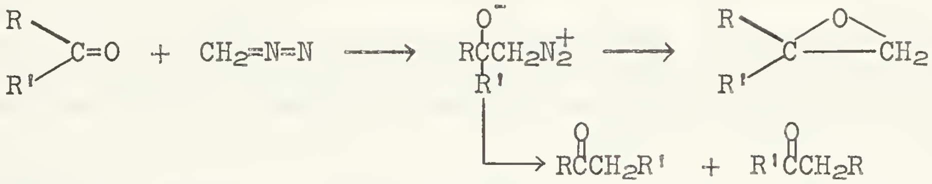
distortion, but that strain due to π-π repulsions may be significantly relieved in the rearrangement. They suggested that the para-substituted ring became more deformed while the meta-substituted became less so, the overall effect being almost even.[24] An actual measure of the deformations involved could be obtained from an x-ray crystallographic investigation of XVII. For the rigid structure XVII, as well as for I and II, appreciable differences in deformation between the crystalline and the solvated state do not seem likely.

Cram and Helgeson examined the reaction of XVIII with diazomethane.[14]



XVIII

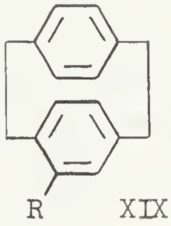
The reaction pathway is:



The reaction gave ring expanded ketonic products. It was believed that the absence of epoxide was a result of a relatively faster rate of the product forming step leading to ketones. This was attributed to a reduction of π-π aryl repulsions in the transition state for ring expansion.[14] It also seems likely that the formation of the epoxide from XVIII would probably involve a significant increase in strain. It is of interest that ketone XVIII was 80% consumed in 10 minutes at 0°, while acetophenone underwent only 44% reaction with diazomethane after four days. Another kinetic study of a ring expansion has been reported.[25]

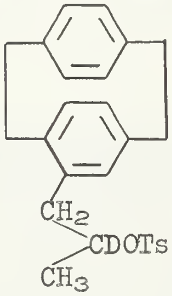
A rate enhancement has been observed in the homolytic aromatic phenylation of [2.2]paracyclophane by Dickerman and Milstein.[26] Strain release, in addition to transannular electronic stabilization, was considered an important factor in lowering the energy for the transition state leading to a cyclohexadienyl type radical intermediate. In the bridge chloroformylation of I possible effects of the deformed aromatic rings were weighed.[27] Other workers studied the influence of aromatic ring deformation on the pk_a's of XIXa and XIXb.[28]

	R
XIXa	OH
XIXb	NH_2



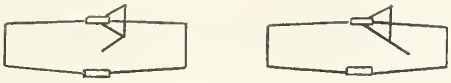
XIX

In recent work, Cram and Harris posed the question of whether the π electrons between the two benzene rings or those on the external faces of the paracyclophanyl nucleus are operative as the neighboring group in the displacement of the tosylate in

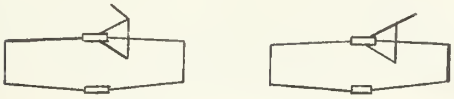


XXα and XXβ

XX.[29] If π electrons between the rings are involved phenonium ion XXI would be formed. The other possibility leads to phenonium ion XXII. To the authors, ion XXII seemed



XXIα and XXIβ



XXIIα and XXIIβ

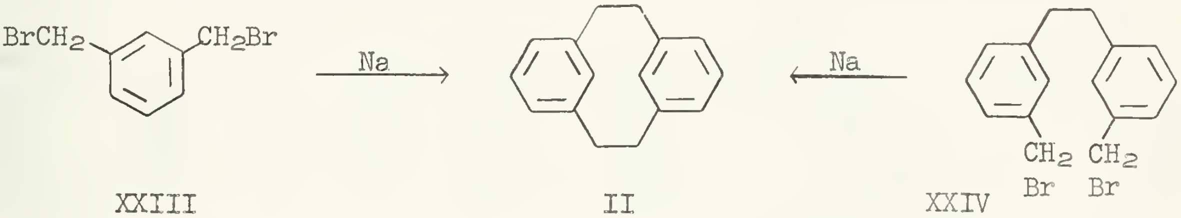
more favorable for two reasons. First, structure XXI is more sterically compressed than XXII. Second, it can be reasoned that the external faces of the benzene rings are more nucleophilic than the internal, since the deformed rings suggest a slight rehybridization of the π electrons toward sp^3. Cram considered it significant that in the crystal structures of [2.2]paracyclophane, the diolefin of [2.2]paracyclophane, and [3.3]paracyclophane the aromatic hydrogens were found to be slightly displaced toward the inside of the molecule from the plane of the aromatic ring to which they are attached. However, as noted by Gantzel and Trueblood,[9] the displacement of the hydrogens may in part be a result of torsion about the ring C-C bonds to C_3 and C_6.

Structures conceivably formed as a result of direct involvement of the transannular benzene ring in bridge ion formation were thought improbable on the basis of prior experimental results.[30]

According to the authors, the ease with which the [2.2]paracyclophanyl nucleus acts as a neighboring group was due to several factors, of which were mentioned strain relaxation and transannular charge delocalization in the transition state for bridge ion formation.[29]

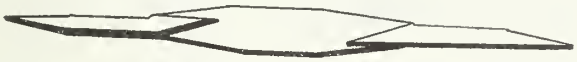
[2.2]METACYCLOPHANE

The synthetic approach to II usually involves either a Wurtz reaction between m-xylyl dibromide (XXIII) and sodium, or a ring closure of XXIV.[2] The latter reaction gives the desired product in 77% yield, while yields from the former are about 33%.

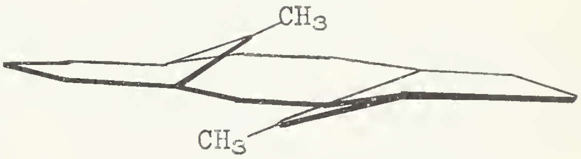


XXIII II XXIV

Brown[31] accomplished the complete x-ray structure determination of II. The benzene rings are arranged step-like, with the rings distorted into a boat shape. The latter deformation is necessary in order to have sufficient separation between the rings. Particularly, as seen in XXV each ring is bent by 11.5° at the inner end and 3.5° at the outer end. The distance between C_8 and C_{16} is 2.7Å, which can be compared to a very inadequate separation of 1.56Å if the rings were planar and undistorted. In addition to the ring distortions, the m-substituent C-C bonds are bent about 15° out of the mean plane of the corresponding benzene rings. Since there are only two molecules per unit cell, the monoclinic space group $P2_1/a$ requires that for an ordered structure each molecule must possess a center of symmetry which in turn coincides with a center of symmetry in the unit cell.



XXV

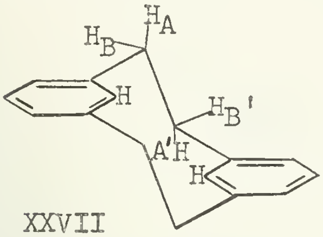


XXVI

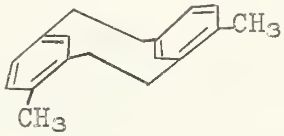
Hanson[32] reported the x-ray crystallographic study of 8,16-dimethyl[2.2]metacyclophane (XXVI). The crystal belongs to the monoclinic space group C2/c with four molecules per unit cell. Again, this information indicates the presence of molecular centers of symmetry, a fact which was demonstrated by the completed structure. The molecular distortions are similar in nature to those of the unsubstituted compound, but greater in value. It is reasonable that this is a result of the greater spacial requirements of the methyl groups.[32] The C_1-C_2 bond, being 1.573Å with an e.s.d. of 0.003Å, was considered by the author to be a good indication of strain. Bekoe and

Trueblood[7] in later work noted that this value agreed very well with the previously mentioned value of 1.569A for the bridge bond length in [2.2]paracyclophane. In Hanson's work, the structure was refined to an R-factor of 0.061 for observed reflections.

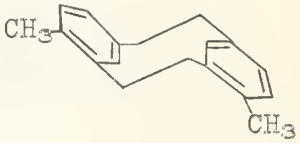
Most spectral interest in II has dealt with n.m.r. studies,[2,33-36] but transannular electronic effects have also been noted.[24] In recent work[35] the n.m.r. spectrum of [2.2]metacyclophane has been studied from -80° to 190°. It was found that the A_2B_2 multiplet centered at $\tau 7.45$ due to the methylene hydrogens in XXVII was temperature independent throughout the range covered. The high energy barrier to inversion has been attributed to nonbonded interactions between the indicated ring hydrogens in XXVII. Existence of this barrier has made possible the optical resolution of XXVIII using XVI.[35]



XXVII



XXVIIIa

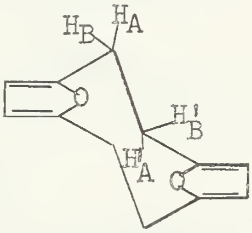


XXVIIIb

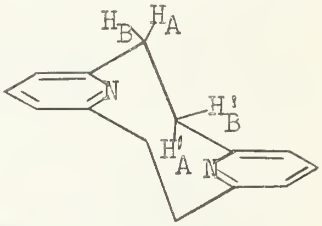
In a communication,[36] Gault, Price, and Sutherland have reported conformational studies of the heterocyclic analogues XXIX and XXX of [2.2]metacyclophane. At 0° in hexafluorobenzene the methylene protons of XXIX give a well-defined A_2B_2 system in the n.m.r. Similarly XXX gave an A_2B_2 multiplet at -40° in deuterochloroform. With each compound the A_2B_2 spectrum collapsed to a broad singlet at the coalescence temperature given in Table I. The results are consistent with the view that transition state interactions for a chair-chair inversion are smaller when the hydrogen atoms are replaced by nonbonded pairs. X-ray crystallographic examination of XXX in earlier work suggested that XXX has a step-like structure resembling that of [2.2]metacyclophane, but only evidence of a preliminary nature was presented.[37]

Table I

Compound	Solvent	τA	τB	Coal. T	Ref.
XXIX	C_6F_6	7.19	7.48	63°	36
XXX	$CDCl_3$	6.72	7.45	13.5°	36
XXVII	CCl_4	7.01	7.97	>>190°	35,36

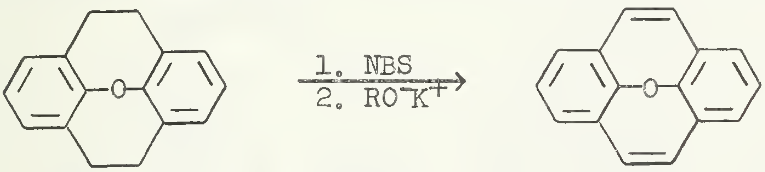


XXIX



XXX

Syntheses of [2.2]metacyclophanes with cis geometry, as compared to the normal trans geometry[38,39] in XXVII, recently have been accomplished. Boekelheide and coworkers synthesized XXXI, which is forced into the cis configuration by the oxygen bridge.[38] In contrast to trans [2.2]metacyclophanes,[2,40] XXXI undergoes benzylic substitution. Treatment with N-bromosuccinimide followed by reaction with potassium t-butoxide produced XXXII. The lack of benzylic character, and thus the failure of II to undergo analogous reaction, has been attributed to the inability of the system to attain the change of geometry required in order to obtain overlap between a developing p orbital and the aromatic π system at a given alpha carbon.[2]

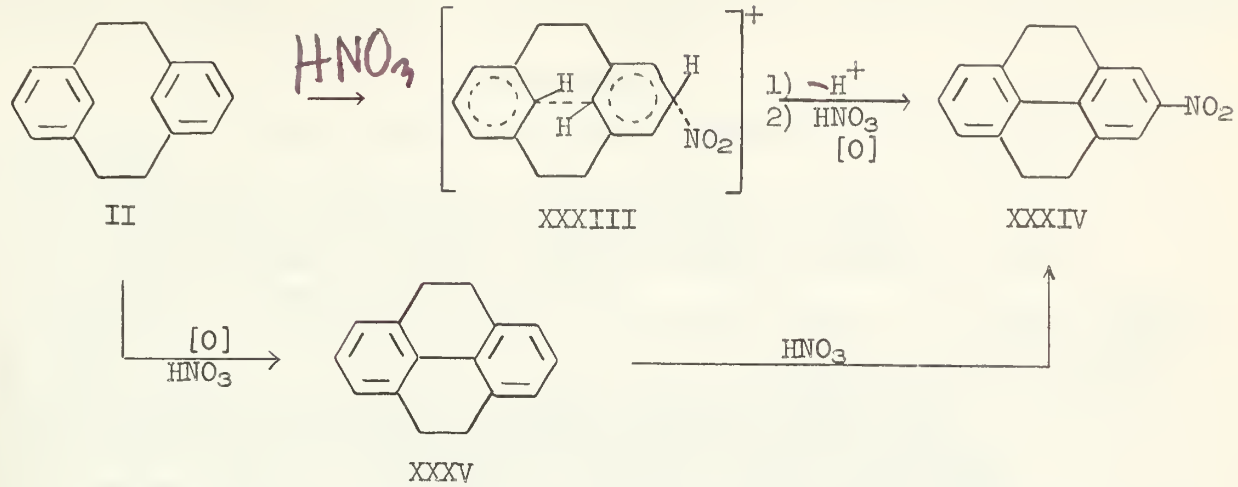


XXXI XXXII

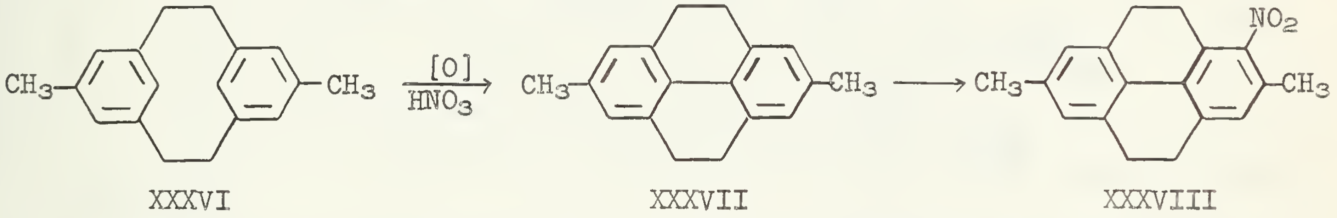
Two important features of the trans [2.2]metacyclophane system are its strain and the close proximity of C_8 and C_{16}. Both are to varying degrees reflected in the reactivity of this system.

Electrophilic substitution invovling transannular reaction has been observed in [2.2]metacyclophane derivatives. Allinger, DaRooge, and Hermann[41] in early work on the nitration of II considered two possible mechanisms. The first was a concerted pathway involving species XXXIII. The other involved initial oxidation to the

tetrahydropyrene XXXV followed by nitration to give XXXIV. It was found that when

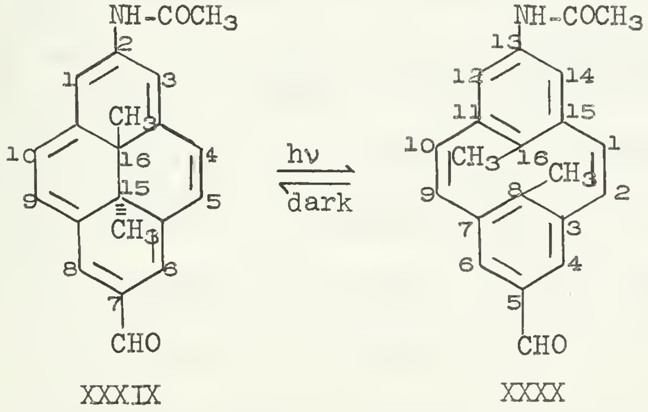


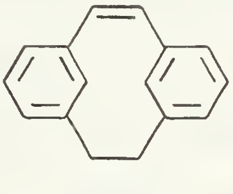
XXXV was independently nitrated, that it also gave XXXIV. Since XXXV could not be isolated in nitration studies of II, the second pathway was not given serious attention until recently.[40] Allinger and co-workers discovered that when XXXVI underwent nitration the product was XXXVIII, but under conditions of partial reaction XXXVII and XXXVIII were obtained in about equal amounts. Furthermore, by extending reaction conditions XXXVII was converted to XXXVIII. With II it was concluded that the intermediate tetrahydropyrene XXXV reacts as rapidly as it is formed to give the observed product XXXIV.[40] Results consistent with those above were obtained by other workers using benzoyl nitrate as the nitrating agent.[42]

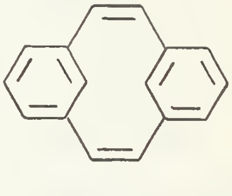


In earlier studies, transannular ring closures to give aromatic derivatives have been effected by aluminum chloride or palladium-charcoal.[2] Ring closure has also been observed upon irradiation of II in the presence of iodine.[43]

An interesting photoisomerization has been reported by Boekelheide and co-workers,[44-47] which seems to be quite general for trans-15,16-dimethyldihydropyrenes. A striking example is provided by XXXIX, which on irradiation with visible light forms the [2.2]metacyclophane-1,9-diene XXXX.[46] The photoisomer XXXX reverts rapidly back to XXXIX in the dark following first-order kinetics with a half-life of a few seconds at room temperature. In contrast, if the substituents at the 2 and 7 positions are replaced by hydrogens the half-life for the dark reaction becomes about two hours at 50°.[45]




XXXXI


XXXXII

Before the above isomerization was known, attempts were made to synthesize [2.2]-metacyclophane-1,9-diene derivatives, all of which failed.[2] A successful synthesis

of [2.2]metacyclophane-1-ene (XXXXI) has recently been accomplished by Boekelheide and Blaschke.[48] However, further reaction of XXXXI with both N-bromosuccinimide and catalytic dehydrogenation produced pyrene instead of the desired 1,9-diene XXXXII.

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DEUTERIUM NUCLEAR MAGNETIC RESONANCE

Reported by Jimmy W. Worley December 18, 1967

Deuterium nuclear magnetic resonance (dmr) has been little investigated relative to proton magnetic resonance (pmr). The physical principles that pertain to dmr and the applications that have been made of it to date show that it can be a valuable tool for the investigation of chemical reactions and molecular structure. In many cases it gives information not available from pmr or other sources.

Work in broad line dmr also often offers advantages over pmr, and this area will also be discussed.

HIGH RESOLUTION DMR--CHEMICAL SHIFTS

In Table 1 are some nuclear properties of protons and deuterons. From the ratio of the magnetic moments and spins of protons and deuterons, the gyromagnetic ratio, γ, of deuterium is calculated to be 6.5144 times smaller than that of protons. Since the chemical shift of an atom is directly proportional to the gyromagnetic ratio,[1] for proton resonances occurring at 40, 60, and 100MHz, the corresponding deuteron resonances are at 6.5, 9.2, and 15.3MHz, respectively.

Table 1. Nuclear properties of protons and deuterons.[1]

Isotope	Natural abundance, per cent	Relative sensitivity for equal number of nuclei: Constant field	Relative sensitivity for equal number of nuclei: Constant frequency	Magnetic moment (units of eh/4πMc)	Spin I (units of h/2π)	Electric quadrupole moment (units of e x 10^{-24} cm^2)
^{1}H	99.984	1.000	1.000	2.79270	$\frac{1}{2}$	--
^{2}H (D)	0.0156	0.00964	0.409	0.85738	1	2.77 x 10^{-3}

Diehl and Leipert[2] compared some proton and deuteron chemical shift data; the results are shown in Table 2.

Table 2. Comparison of dmr and pmr chemical shifts of some pairs of compounds.[2]

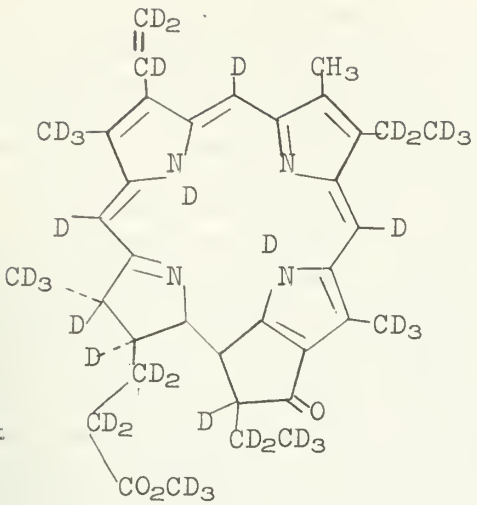
Chemical Shift Between	H-Resonance	D-Resonance
Chloroform and acetone	5.92 ppm	5.91 ppm
Water and acetone	2.84	2.87
Benzene and acetone	5.14	5.08
Benzene and water	1.75	1.74
Chloroform and water	2.56	2.61
Chloroform and benzene	0.82	0.86

Montgomery, Clouse, Crelier, and Applegate[3] have reported that the chemical shifts of some allylic, olefinic, and α-keto deuterons relative to deuterated internal standards differed from the chemical shifts of the corresponding proton compounds relative to the corresponding proton standards by no more than 0.1 ppm. Doughtery, Norman, and Katz[4] reported that the chemical shifts of five different deuterons in the dmr of methyl deuteriopheophoribide a (1) differed from their proton counterparts by no more than 0.05 ppm.

These results would seem to indicate that one could qualitatively use the chemical shift data that has been collected on proton compounds for dmr studies; that is, that no substantial changes are brought about in the magnetic susceptibility of a compound by substituting deuterons for the protons.

This is further supported by consideration of deuterium isotope effects in pmr and F^{19} nmr and the explanations that have been proposed for the effects.

Tiers reported that the protons in the $-CH_2D$ group of α-deuterotoluene[5] are 0.015 ± 0.002 ppm more shielded than are those in the $-CH_3$ group of deuterium-free toluene or of p-deuterotoluene, and also that in F^{19} nmr the fluorine nuclei[6] in the



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$-CF_2D$ group of n-C_3F_7D are 0.60 ± 0.05 ppm more shielded than those in the $-CF_2H$ group of n-C_3F_7H. The direction of the shift in both cases qualitatively represents a greater electron-donating power for deuterium than for hydrogen, which is indicated also by the kinetic isotope effect of deuterium.[7]

Gutowsky[8] noted that in the pmr of acetone-d_5 the proton of the $-CHD_2$ group is 0.034 ± 0.001 ppm (1.35 ± 0.02 Hz at 40 MHz/sec) more shielded than the protons of the $-CH_3$ group in undeuterated acetone. He explained the effects qualitatively on the basis of a simple electrostatic model.

Earlier, Ramsey[9] had predicted these isotope effects on the nuclear magnetic shielding by some sophisticated calculations on diatomic molecules which were based on differences in zero-point vibration and centrifugal stretching of the molecules. These two quantities affect the internuclear spacing of the atoms involved and therefore the magnetic shielding. They are different for hydrogen and deuterium because of the mass differences of the two, the effects of which are further enhanced by the anharmonicity of the wave functions (for the zero-point vibration, a harmonic term and a cubic term are usually included).

Marshall[10] calculated from quantum mechanical considerations of zero-point vibrations that the deuterium atoms of D_2 should be 0.055 ppm more shielded than the hydrogen atoms of H_2 and 0.030 ppm more shielded than the atoms of HD. These values are very close to the observed isotope effects we have noted.

SPIN-SPIN COUPLING IN DMR

In systems differing only in terms of isotopic substitution,[1] $J_{DD} = J_{HH}/(6.51)^2$ and $J_{DH} = J_{HH}/6.51$. The coupling between non-equivalent protons is generally less than 20 Hz. Therefore the maximum value of coupling between non-equivalent deuterons is 0.5 Hz. Since the natural line width of deuterium resonances is usually greater than this value, deuteron-deuteron coupling has thus far not been observed.

Diehl and Leipert[2] have reported coupling of deuterons with protons, carbon-13, and phosphorus-31. They reported J_{HD} for the $-CHD_2$ group of acetone-d_5 to be 2.18 ± 0.03 Hz. This value should agree with J_{HD} determined from the proton spectrum, which is reported as 2.27 ± 0.05 Hz.[11]

Diehl and Leipert's $J_{C^{13}D}$ values from some dmr spectra are compared with the predicted and found values of $J_{C^{13}H}$ in Table 3.

Table 3. Comparison of $J_{C^{13}H}$ values determined from pmr with those calculated from dmr.[2]

Compound	$J_{C^{13}D}$ (Hz)	$6.5144 J_{C^{13}D}$	$J_{C^{13}H}$
Acetone	19.48 ± 0.05	126.9 ± 0.3	126 ± 1
Benzene	24.22 ± 0.10	157.8 ± 0.7	159 ± 1
Chloroform	31.95 ± 0.05	208.1 ± 0.3	209 ± 1

QUADRUPOLE EFFECTS IN DMR

Nuclei with spin I greater than $\frac{1}{2}$ possess an electric quadrupole moment, which means physically that the nuclear charge is not spherically symmetric.[12] Expressions describing the electric quadrupole phenomenon are found in common sources,[12,13] and the physical evidence for it is provided by agreement of theory with the fine structure in microwave spectroscopy[14] and by the nuclear quadrupole resonance experiment.[15,16]

The existence of an electric quadrupole moment in deuterium and determination of its value were reported by workers in the 1940's.[17]

The interaction of the quadrupole moment with the fluctuating electric field gradient produced at the nucleus by the varying charge distribution[15,18] of the atom's environment provides a very efficient mechanism for relaxation of the nuclei, and therefore a very short spin-lattice relaxation time results.[19] This mechanism is so facile that even for the deuteron, which has the smallest known electric quadrupole moment, it is the dominant mechanism for spin-lattice relaxation.[19]

As a result of the electric quadrupole interaction, the spin-lattice relaxation time for a deuteron is much shorter than that for a proton,[15] and in consequence broader lines are observed for deuterium resonances than for proton resonances. This is explained in the following manner: the natural width (w) of a spectral line is inversely proportional to the average time (t) that the system spends in the excited state[15] ($w \propto 1/t$). As the lifetime of the excited state becomes very short, then, by the Uncertainty Principle ($\Delta E \Delta t \geq h$), the uncertainty in the energy of that state becomes very large. When ΔE is large, a wide range of frequencies is absorbed in transitions, resulting in a broad line.

Diehl and Leipert reported that for deuterons the spin-lattice relaxation time (T_2) is approximately equal to the spin-spin relaxation time (T_1) and is dependent on the electric quadrupole interaction and the correlation time (τ_c).

$$1/T_1 \simeq 1/T_2 = 3/8[(eQ/h)\partial^2 V/\partial z^2]^2 \tau_c$$

$$\tau_c = 4\eta a^3/3kT$$

where η = viscosity, a^3 = molecular volume, and T = absolute temperature.

A discussion of the theory of quadrupole relaxation is given in a work by Abragam.[20]

Diehl and Leipert found line widths of 0.5-1.2 Hz for the deuterium atom of the -OD group of some small deuterated alkyl alcohols. Montgomery, Clouse, Crelier, and Applegate[3] found line widths at half-peak height of 1-4 Hz for some partially deuterated compounds and 0.6-0.8 Hz for some fully deuterated ones. The compounds they studied will be discussed later. Doughtery, Norman, and Katz[4] observed line widths of 2-7 Hz in the dmr of methyl deuteriopheophorbide a (1) and of chlorophyll a-d_{72}. Large, unsymmetrical compounds as these would be expected to have large correlation times and therefore to give broad resonance lines.

EXPERIMENTAL DETERMINATION OF DEUTERIUM RESONANCES

Deuterium resonances reported have been at 6.536,[21] 7.65,[2] 9.201,[3] and 15.338[4] MHz. Diehl and Leipert's work was at 7.65 MHz, using a 1 cm insert ($\simeq$ 2 ml) for most of their work. They found that operation in the dispersion mode gave better results than operation in the absorption mode. They found that signals from natural abundance deuterium (1.56×10^{-2}%) in acetone were barely detectable (Fig. 1). However, they could detect 0.1% D_2O in H_2O (Fig. 2), and obtained results comparable to those in proton resonance with 1 to 5 ml of sample solution of 100%-deuterium-enriched functional groups, as the $-CD_3$ group of p-CH_3-Ø-SO_2-NH-CD_3 (Fig. 3). Their dmr of pyridine-d_5 in the absorption mode is compared with its proton counterpart in Fig. 4.

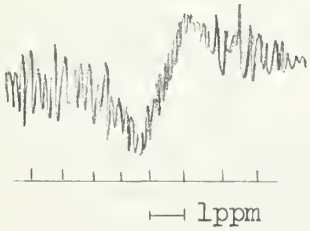


Fig. 1. Dmr signal from natural abundance deuterium in acetone

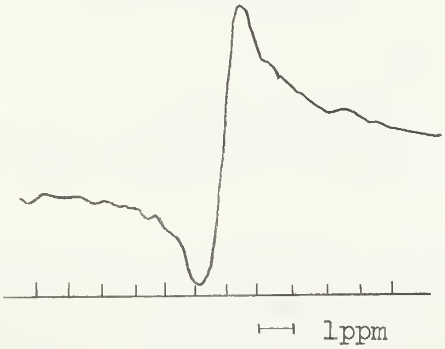


Fig. 2. Dmr signal from 0.1% D_2O in H_2O

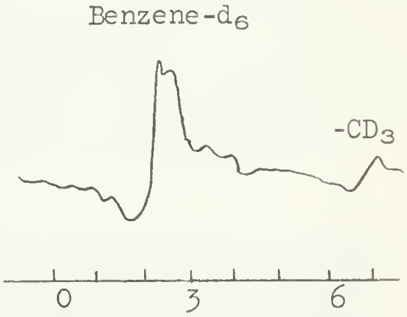


Fig. 3. Dmr signal from $-CD_3$ group of p-CH_3-Ø-SO_2-NH-CD_3 (external reference: benzene-d_6)

Montgomery, et al., operating at 9.201 MHz, could detect natural abundance signals in water and acetone in the dispersion mode, using a 3 ml sample (15 mm insert). In the absorption mode they could detect signals from 3 ml of 0.1% solutions of chloroform-d_1, acetone-d_6, and D_2O. They obtained approximately 20:1 or better signal-to-noise ratios for 1 to 3 ml of 5 to 30% solutions of fully-deuterated molecules. Partially deuterated compounds required more sample for comparable signals.

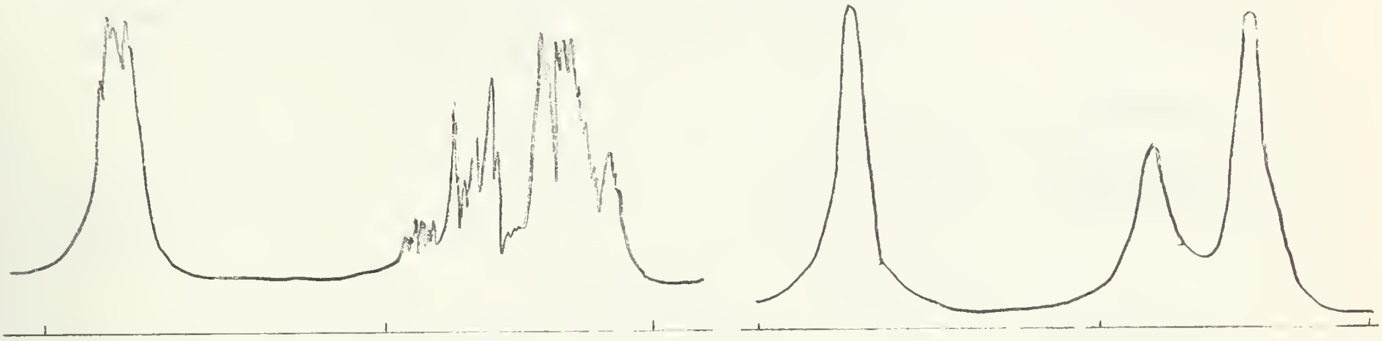


Fig. 4
a. Pmr spectrum of pyridine.[2]
b. Dmr spectrum of pyridine-d_5.[2]

Proton compounds do not give signals in dmr and therefore can be used as solvents. Alternately, a deuterated compound can be used for both solvent and internal standard. Also, sym-tetramethylsilane-d_4 is available as a reference.

All workers quoted have reported that, as in pmr, spinning of the sample leads to better resolution. Slow passage is also helpful.

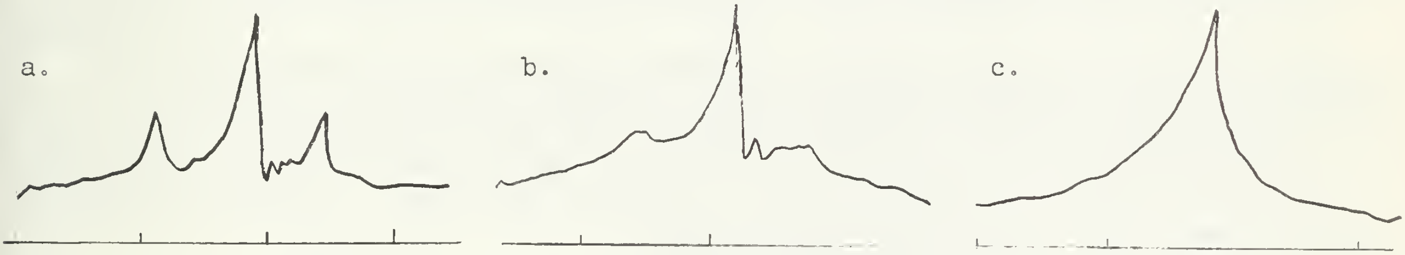
The scale can be calibrated by the normal sideband method.

Diehl and Leipert used an ingenious method of proton-deuteron decoupling in partially-deuterated acetone. Addition of paramagnetic species to an nmr sample provides an extremely facile method for spin-lattice relaxation.[22] Since the relaxation time is inversely proportional to the gyromagnetic ratio,[22] proton relaxation times are diminished by a factor of about 40 times more than deuteron relaxation times.

In the dmr spectrum of acetone-d_5, a singlet appears for the $-CD_3$ group and a doublet for the $-CHD_2$ group, in which the deuterons are coupled to the proton.

If a paramagnetic ion, as Mn^{+2}, is added to the solution, the doublet lines will broaden much more than the singlet. At a certain concentration of ion, the line widths of the doublet will exceed the value of the coupling constant, J_{HD}, and the doublet will no longer be observable. Thus, the dmr of a partially deuterated compound is easily simplified by proton-deuteron decoupling. This procedure is illustrated for the acetone example in Fig. 5.

Fig. 5. Proton-deuteron decoupling in acetone-d_5. The doublet is from the $-CHD_2$ group. The singlet between the doublet lines is the signal from the $-CD_3$ group.



Concentration of Mn^{+2}: a. 0.0; b. 1.65×10^{18} Mn^{+2}/ml (2.74×10^{-3} molar); c. 1.2×10^{19} Mn^{+2}/ml (19.9×10^{-3} molar).

SOME APPLICATIONS OF DMR

Diehl and Leipert suggested that dmr should be helpful in the study of kinetic problems. For weak deuteration it should be more precise than pmr, since the accuracy of measuring an appearing D-resonance line will be better than the measuring of a slight decrease in the proton resonance line. Further, for deuteration at an unknown position of a molecule with a complex proton spectrum, the deuterium spectrum will be much simpler and easier to interpret.

Montgomery, Clouse, Crelier, and Applegate used dmr to investigate the mechanism of the reaction of 1-chlorocyclohexene and 1-chlorocycloheptene with phenyllithium to give 1-phenylcyclohexene and 1-phenylcycloheptene, respectively. Proposed mechanisms were direct displacement, cycloallene formation, and cycloalkyne formation. It was hoped that by using deuterated starting material, the dmr of the product would help determine which of these three pathways was correct.

For the reaction of 1-chlorocycloheptene-2,7,7-d_3 (2), the possible pathways and resulting deuterium distributions are shown in Fig. 6.

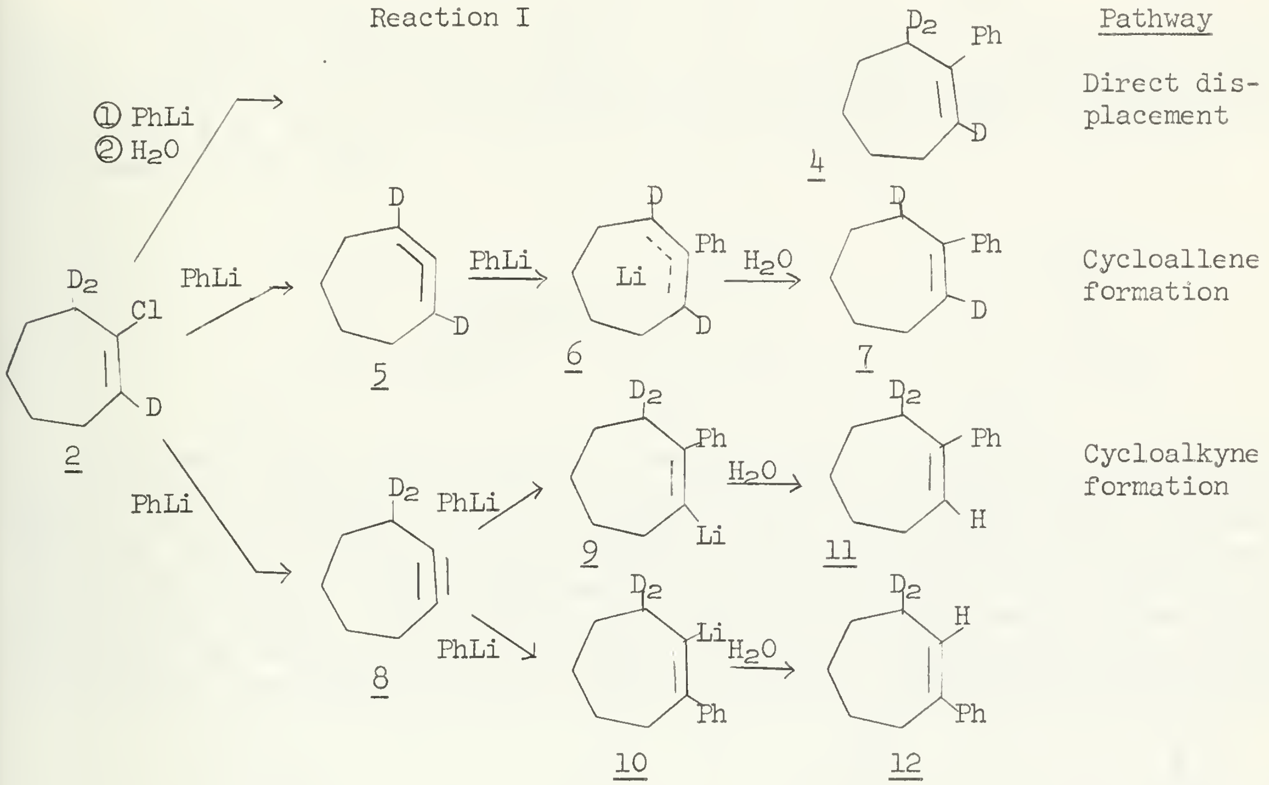


Fig. 6. Pathways and resulting products for reaction of phenyllithium with 1-chlorocycloheptene-2,7,7-d_3 and hydrolysis with water.

From the pmr of the product, it was determined that 0.17 $\pm$ 0.02 deuteron and 1.96 $\pm$ 0.12 deuterons were present in the olefinic and saturated ring positions, respectively. The positions of the saturated deuterons could not be assigned exactly from the proton resonance, though, because the saturated proton region consisted of continuous complex absorption extending from 1.1 to 2.9 ppm downfield from TMS. But the deuterium distribution tentatively favored alkyne formation over the other two possibilities.

The same information was obtained from the deuterium spectrum of the product, but, in addition, the specific locations of the saturated deuterons could be assigned. The saturated ring portion of the dmr spectrum consisted of two overlapping peaks of approximately equal intensity (Fig. 7) at 2.50 and 2.80 ppm downfield from sym-tetramethylsilane-d_4. These were assigned to the 3-position of compound 12 and the 7-position of compound 11. Thus, the product contained an average of one deuteron in each of the allylic positions, in agreement with the cycloalkyne pathway.

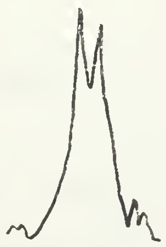


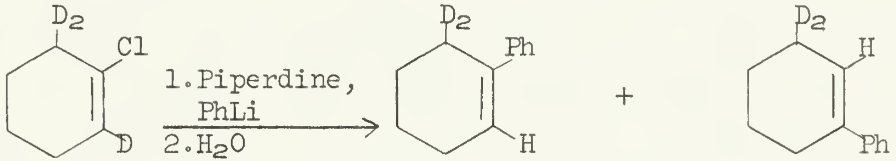
Fig. 7. Dmr in saturated region of product from reaction (I)

The reaction was also run using 1-chlorocyclohexene-2,6,6-d_3 and piperdine as catalyst. Piperdine is known to catalyze the reaction of phenyllithium with aryl halides, through a benzyne intermediate, and it was thought that it might also act as a catalyst in this case. Huisgen[23] has proposed a mechanism for

piperdine's role as catalyst for the aryl halide system:

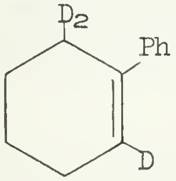
1) $PhLi + C_5H_{10}NH \rightarrow PhH + C_5H_{10}NLi$
2) $C_5H_{10}NLi + PhCl \rightarrow C_6H_4 + C_5H_{10}NH + LiCl$
3) $PhLi + C_6H_4 \xrightarrow{k_3} PhC_6H_4Li$
4) $C_5H_{10}NLi + C_6H_4 \xrightarrow{k_4} C_5H_{10}NC_6H_4Li$
5) $PhC_6H_4Li + C_5H_{10}NH \rightarrow Ph\text{-}Ph + C_5H_{10}NLi$
$k_3/k_4 = 4.4$

Without piperdine, the cycloheptyl system was run at 150° for 1.3 hours while, for the cyclohexyl system with piperdine, the reaction went comparably at 35°, but with 155 hours reaction time. Reaction in the cyclohexyl system without piperdine was negligible at 35°. If the reaction went through an alkyne intermediate, as in the heptyl case, the products would be 1-phenylcyclohexene-6,6-d_2 (14) and 1-phenylcyclohexene-3,3-d_2 (15).



13 14 15

For the product in this case, 0.1 deuteron and 2.0 deuterons were found in the olefinic and saturated ring positions, respectively, pointing to the alkyne mechanism again. But, in contrast to the cycloheptyl case, the dmr showed only a single peak (Fig. 8a) in the saturated deuteron region. The peak occurred at 2.33 ppm and had a line width of 7 Hz. For comparison, 1-phenylcyclohexene-2,6,6-d_3 (16) was synthesized independently. Its dmr spectrum, which would be expected to be very similar to that of the saturated deuterons of compound 14, showed a singlet (Fig. 8b) at 2.36 ppm and line width of 4 Hz. Thus, if there were deuterons in the 6-position



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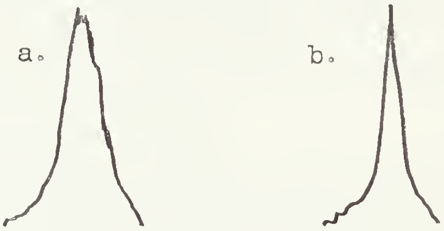
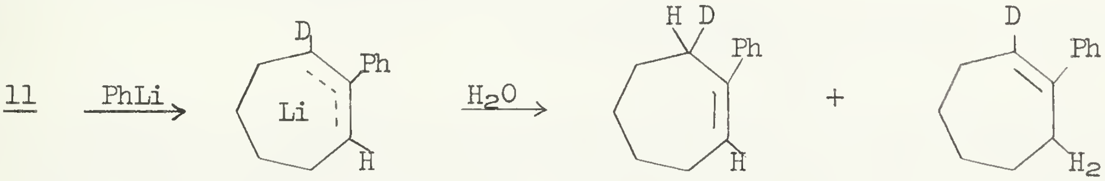


Fig. 8.

of the product, there must also be deuterons in a position at slightly different field. The number of saturated ring deuterons and their chemical shift supports an alkyne intermediate over the other two possibilities considered, but the evidence is not conclusive.

Montgomery, et al., attributed the 0.17 and 0.10 olefinic deuteron in the C_7 and C_6 cases, respectively, to one of two possibilities. Compounds 9 and 10 could have picked up deuterons from starting materials, or compounds 11 and 12 could have undergone protoprotic rearrangement.



LIQUID CRYSTAL STUDIES USING DMR*

Parameters important in the description of the high resolution nmr of nuclei of spin ½ are shielding constants, coupling constants, and values of dipole-dipole coupling

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*The theory of liquid crystals and their nmr presented here is taken from references 21, 24, 25, and 26.

between nuclear spins. In liquids and gases the dipole-dipole coupling, whose root mean square value may be 10,000 cps, vanishes due to rotational and translational motion. This allows study of the fine structure due to chemical shifts and indirect coupling via the electrons, since these phenomena, though much smaller, do not vanish.

In solids, the line width is usually dominated by the dipole-dipole interaction, and the fine structure is not seen. A dipolar interaction is proportional to the inverse cube of the internuclear distance, and therefore study of the interaction gives valuable information on crystal parameters.

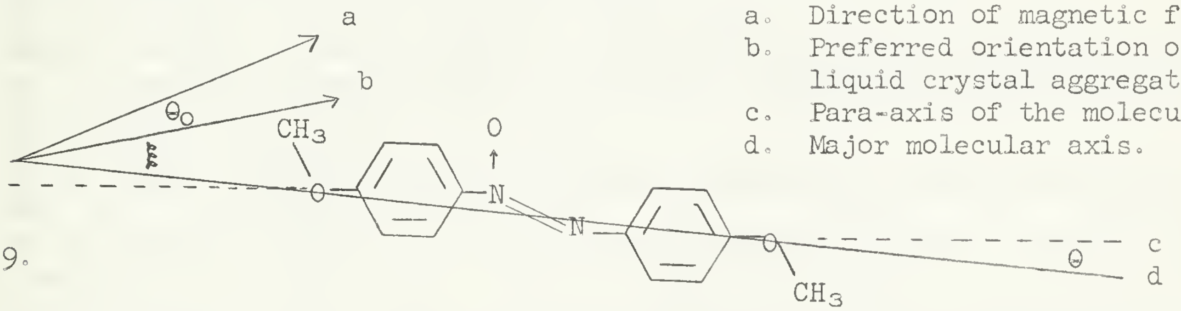
Liquid crystals are substances having properties intermediate between those of an isotropic liquid and a crystalline solid. They exist in one of three types of phases. Of the three, the nematic phase has been found the most useful in nmr studies. Substances that exhibit nematic phases are usually long and flat molecules and contain groups as phenyl, azoxy, and carboxyl which can exert strong intermolecular attractions. These attractions cause the molecules to form aggregates of up to 10^6 molecules with major molecular axes parallel. If a nematic phase is placed in a strong magnetic field, the molecules orient so as to align their axes of minimum diamagnetic susceptibility with the applied field, resulting in a very high degree of orientation, but differing from crystalline structure in that the molecules are still in continuous motion relative to one another. This motion minimizes intermolecular dipolar interactions and allows observation by nmr of sharp signals arising solely from intramolecular dipolar interactions.

For compounds having nuclei with an electric quadrupole moment, as deuterium, another, larger, interaction occurs, which can be observed by dmr. This is the interaction of the quadrupole moment with the electric field gradient, as mentioned previously; but the electric field gradient in this case has only intramolecular contributions because intermolecular terms are averaged to zero by the molecular motions. The perturbation of the deuteron Zeeman levels that arises from this interaction gives rise to a doublet in the dmr spectrum of a specific deuteron. The magnitude of the splitting, ΔH, is given[21] by $\Delta H = \frac{3}{4}(e^2qQ/\mu_D)(3\cos^2\theta-1)$, where q = the electric field gradient experienced by the deuteron quadrupole moment Q, μ_D is the deuteron nuclear moment, and θ is the angle between q and the magnetic field direction.

The expression $(3\cos^2\theta-1)$ can be defined in terms of parameters which are directly related to the liquid crystal's motion and structure. This allows the equation to be rewritten as

$$\Delta H = 3/2(e^2qQ/\mu_D)(3/2\cos^2\gamma-\tfrac{1}{2})(3/2\cos^2\phi-\tfrac{1}{2})S$$

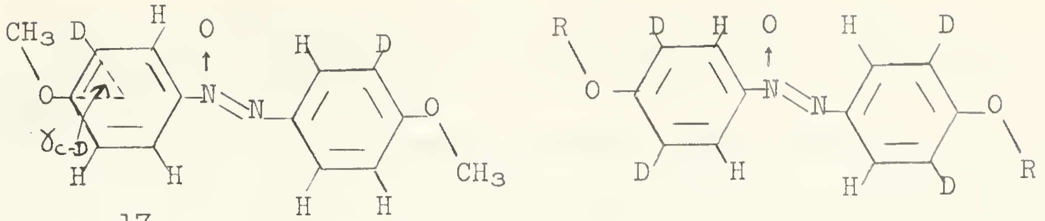
where γ is the angle between the C-D bond direction and the para axis of the molecule, ϕ is the angle between the para axis and the major molecular axis, and S, the degree of microorder, is equal to $(3/2\cos^2\xi-\tfrac{1}{2})$, with ξ being the angle of inclination of a particular molecular axis to the preferred orientation, caused by thermal oscillations. In Fig. 9, the axes and angles are shown for p-azoxyanisole (PAA).



a. Direction of magnetic field.
b. Preferred orientation of the liquid crystal aggregates.
c. Para-axis of the molecule.
d. Major molecular axis.

Fig. 9.

From the observed splittings and assumptions on the axes of the system, Rowell, Phillips, Melba, and Panar[21] calculated S values at different temperatures for compounds as PAA-d_2 (17), PAA-d_4 (18), and p-azoxyphenetole-d_4 (PAP-d_4) (19). By comparison of these values with those obtained from the dipolar interactions of the protonated analogs, the data could be fitted to indicate that the angle γ_{C-D} (see Fig. 10) at the temperatures studied (115-134°) was 57.5-58.0° rather than the assumed hexagonal angle of 60°. The angle approached 60° at the lower temperature.



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18 R = CH_3

19 R = C_2H_5

Fig. 10.

PAA-CD_3 (20) gave only a singlet doublet in its dmr spectrum, indicating rapid rotation of the -CD_3 group to make the deuterons equivalent. The size of the splitting was very small (from 3.79 gauss at 113.5° C to 2.75 gauss at 132° C). The temperature dependence of the splitting indicates increased motion of the -CD_3 group with increasing temperature to give a partial averaging-out of the electric field gradient (recall that in isotropic liquids molecular motions completely average the field gradient). It was calculated, again with the help of results of dipolar studies on the protonated analog, that the small size of the splitting indicated that the ether angle α (see Fig. 11) was 123.1° at 113.5° C.

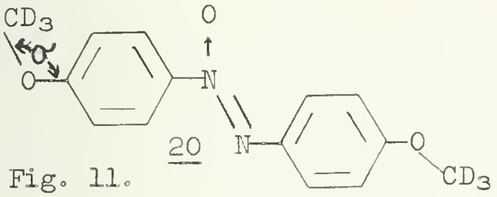

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Fig. 11.

Replacing the -CD_3 group of compound 20 by larger alkyl groups had the effect of adding one more doublet for each additional methylene group, again indicating fast enough motion to make the two deuterium atoms in each methylene group equivalent. But from the size of the splittings (3.79 gauss at 113.5° C for PAA-CD_3 as compared with 79.1 gauss for the -CD_2- group of PAP-C_2D_5), it was concluded that, while the terminal methyl groups are allowed rapid rotation, the methylene groups must be limited to small amplitude vibrations.

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OXIDATIONS WITH PEROXYTRIFLUOROACETIC ACID - BORON FLUORIDE

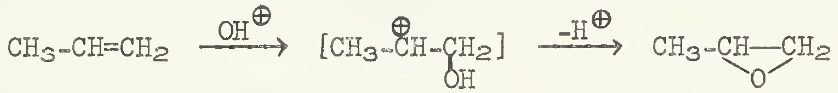
Reported by James H. Klug December 21, 1967

INTRODUCTION

This seminar will deal with oxidations in aromatic systems using peroxytrifluoroacetic acid - boron fluoride and the formation of ketones from substituted olefins using the same reagent. A discussion on the question of the existence of "positive hydroxyl" in peracid oxidations will also be reviewed.

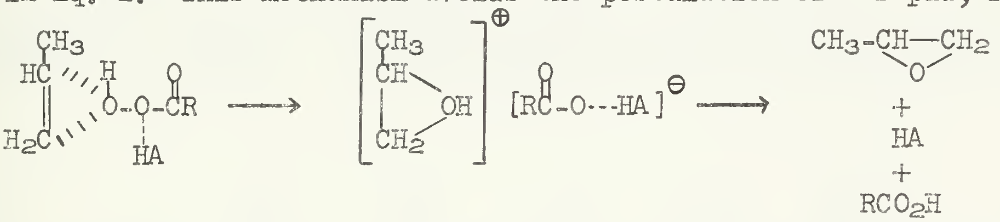
ON THE QUESTION OF POSITIVE HYDROXYL

There are numerous and varied reactions of organic peracids reported in the literature. Swern[1] points out that it is evident that the peracid acts as an electrophilic reagent. It was early proposed,[2-6] since peracid reactions are subject to general acid catalysis, that the attacking species in peracid oxidations is the electropositive hydroxyl cation, OH$^{\oplus}$, as depicted in Eq. 1. Swern,[1] however, advocated a mechanism which involves direct formation of the conjugate acid of the epoxide by donation of OH$^{\oplus}$ to the olefin by the peracid-general acid complex as shown in Eq. 2. This mechanism avoids the postulation of a rapid, reversible OH$^{\oplus}$ formation from the peracid and general acid followed by slow attack of OH$^{\oplus}$ on the double bond. Several workers still feel OH$^{\oplus}$ to be the attacking species in epoxidations and hydroxylations using peracid.[7-10] Davidson and Norman,[11] on the other hand, felt that the real problem was whether the peroxy-bond underwent heterolysis to form OH$^{\oplus}$ or homolysis to form ·OH in peracid oxidation. Heterolytic cleavage of the peroxy bond has been assumed by many workers, since the order of reactivities and positions of attack in aromatic oxidations using peracids are characteristic of electrophiles. But the hydroxyl radical has since been shown to possess electrophilic character.[12-14] In a comparison of results obtained in the oxidation of anisole, toluene, and fluorobenzene with peroxytrifluoroacetic acid with those for homolytic hydroxylation, it has been found that the characteristics of peroxytrifluoroacetic acid as a hydroxylating agent are different from those of the hydroxyl radical.[11,12] Notably, fluorobenzene gives an appreciable amount of the meta-derivative when reacted with hydroxyl radical while no formation of a meta-derivative can be detected with the peracid; the spread in relative reactivities is also far greater for the peracid than for the radical. Roitt and Waters[5] in 1949 also rejected free radical theories of oxidation by perbenzoic acid because two hydrocarbons they studied, tetralin and indane, which were easily autoxidized, were among the least prone to attack. In contrast, they point out, oxidative attack seems to be preferred at the reactive centers of the aromatic nuclei rather than at the attached methylene groups. This is in full accord with Swern's view[15] that the peracids tend to provide cationic hydroxyl groups rather than hydroxyl radicals. Hamilton and Friedman[16] came to the same conclusion in their experimentation concerning the hydroxylation of anisole with hydrogen peroxide. Another viewpoint, expressed by Kwart and Hoffman[17] in 1966, suggested a 1,3-dipolar mechanism for the reaction of olefins with peracids as shown in Scheme 1. This mechanism is formulated on the basis of strong similarities noted between many of the reactivity parameters and general kinetic characteristics of the peracid epoxidation mechanism with those of the 1,3-dipolar addition examples studied. However, conclusive experimental evidence supporting this mechanistic pathway is to date lacking. Hart and co-workers in their work with oxidations of



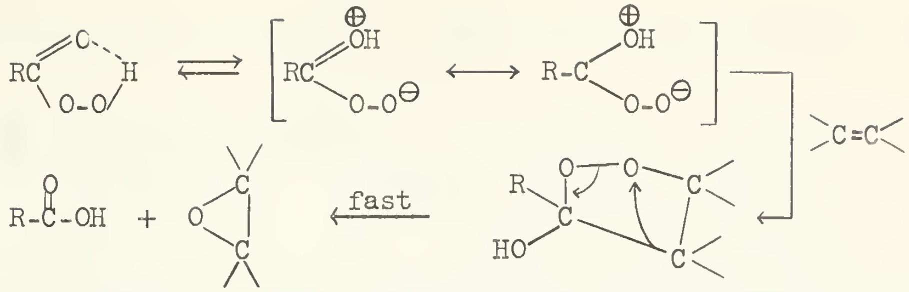
$$CH_3\text{-}CH{=}CH_2 \xrightarrow{OH^{\oplus}} [CH_3\text{-}\overset{\oplus}{C}H\text{-}\underset{OH}{C}H_2] \xrightarrow{-H^{\oplus}} CH_3\text{-}CH\text{—}CH_2 \; (\text{-O-})$$

Eq. 1



Eq. 2

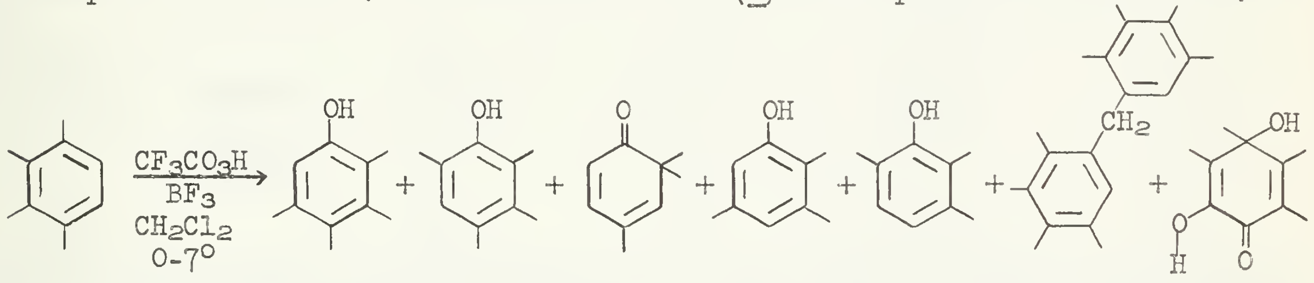
Scheme 1



aromatic hydrocarbons considered peroxytrifluoroacetic acid to be an excellent source of positive hydroxyl because the trifluoroacetate anion is an excellent leaving group.[18] They also reasoned that coordination of a Lewis acid such as boron fluoride with peroxytrifluoroacetic acid might facilitate departure of an ionic electrophilic hydroxyl from the latter and furnish a potent oxidant under mild conditions.[19] Evidence, therefore, seems to indicate that positive hydroxyl, or some complexed form of it, is the attacking species in peracid oxidations using peroxytrifluoroacetic acid - boron fluoride.

OXIDATION OF METHYL BENZENES

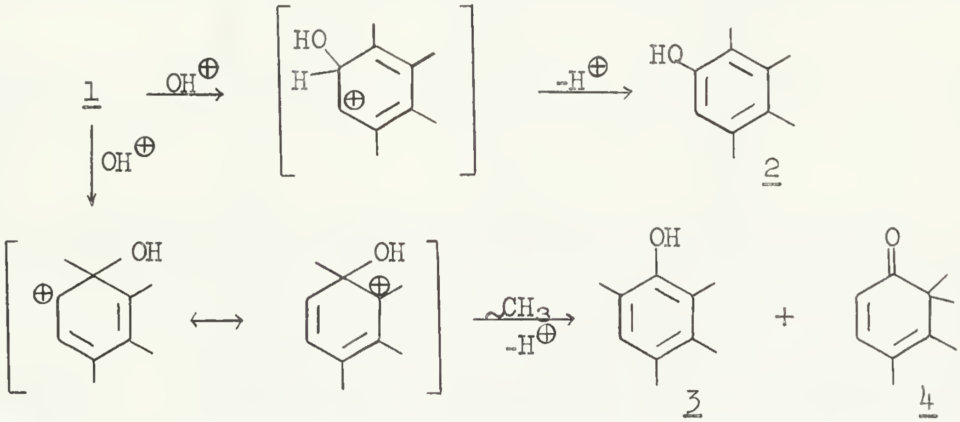
Hart and co-workers[6,19,20] in 1963 studied the reaction of prehnitene (1) with peroxytrifluoroacetic acid, with and without boron fluoride. With boron fluoride the peracid is used with 86% efficiency; without it, only 30% of the theoretical amount of prehnitene is oxidized. Boron fluoride therefore seems to play an integral part in the peracid oxidation. In the oxidation of (1) seven products are obtained.



1 2(9.1%) 3(3.6%) 4(1.8%) 5(14.5%) 6(5.4%) 7(23.6%) 8(--)

Prehnitol (2), isodurenol (3), and 4,5,6,6-tetramethyl-2,4-cyclohexadienone (4) are reasoned as being formed by attack of $OH^{\oplus}$ at C-1 or C-6 in prehnitene as depicted in Scheme 2. Isolation of dienone (4), Hart felt, provides excellent evidence that the

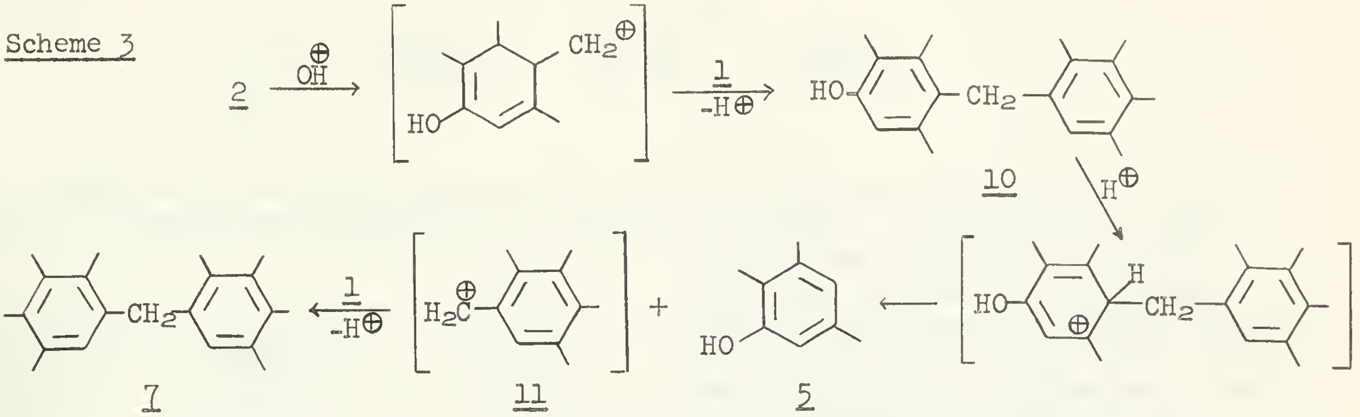
Scheme 2



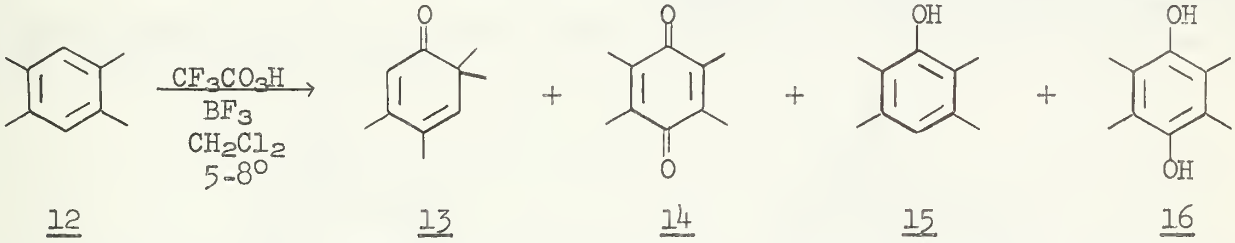
hydroxylation involved cationic rather than radical intermediates, since the Wagner-Meerwein rearrangement necessary for its formation is not unusual, whereas a free radical rearrangement of this type would be exceptional.[6] The formation of C_{10} product (8) was observed in the oxidation of (1) without boron fluoride but was not observed when boron fluoride was used. The structure postulated for (8) rests on a molecular weight determination by mass spectroscopy and formulation of a mechanistically plausible pathway from (1), but its structure is still uncertain. The formation of 2,3,5- and 2,3,6-trimethylphenols, (5) and (6), results supposedly from

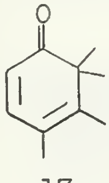
loss of the 4-methyl group from (2) and (3), respectively. The formation of (5) and (7) is mechanistically pictured in Scheme 3. Hydride abstraction from the hydroxylated ring (2) is facilitated by resonance stabilization of the resulting 4-hydroxybenzyl cation (9). Intermediate (10) is not isolated but debenzylates to (5) and (7) where the hydroxyl group in (10) helps to facilitate debenzylation. Similarly, a scheme starting with (3) accounts for the formation of (6). The yields of (5), (6), and (7) are very much lower when boron fluoride is omitted which suggests that either boron fluoride is involved in the hydride transfer, or a more effective oxidizing agent is produced with boron fluoride present.[6]

Scheme 3



The oxidation of durene (12) with peroxytrifluoroacetic acid - boron fluoride in methylene chloride at 5-8° affords four products.[21] The major product obtained is 3,4,6,6-tetramethyl-2,4-cyclohexadienone (13) in yields as high as 78% based on converted durene. The structure of (13) was deduced from its analysis, spectral properties, and chemical transformations. There are six possible x,x,6,6-tetramethyl-2,4-cyclohexadienones that can theoretically be formed in this reaction and all except (13) and (18) were ruled out on the basis of spectroscopic data. The Diels-Alder adduct of the dienone and maleic anhydride affords a crystalline product which has an nmr spectrum consistent with structure (22). Two doublets (three protons each, J=1.0 cps) at τ 8.15 and 8.10 correspond to the two allylic methyl groups. This fixes the positions of the methyls at C-3 and C-4 in the original dienone (13) and rules out dienone (18). Duroquinone (14), durophenol (15), and tetramethyl hydroquinone (16) were formed in relatively small yield and identified by comparison of infrared spectra and vpc retention times with those of authentic samples. Products (14), (15), and (16) are readily accounted for by electrophilic attack of OH⊕ on durene at an unsubstituted ring position. Dienone (13) is postulated as arising from attack at a methyl bearing carbon followed by methyl migration and loss of hydrogen as depicted in Scheme 4.

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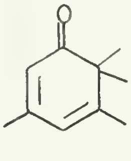
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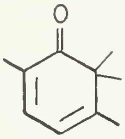
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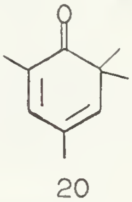
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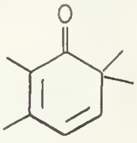
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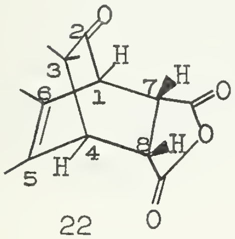

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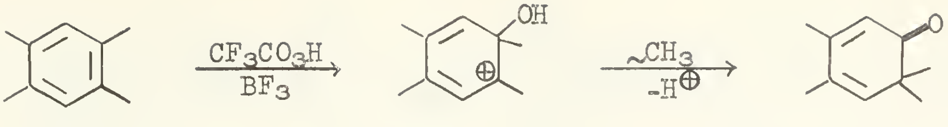
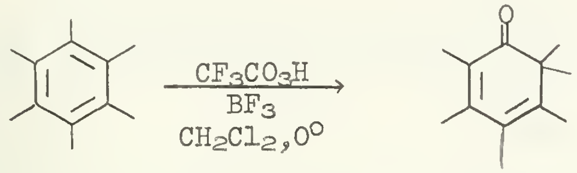
Scheme 4



12 13

Oxidation of hexamethylbenzene (23) with peroxytrifluoroacetic acid - boron fluoride in methylene chloride at 0° affords one product, hexamethyl-2,4-cyclohexadienone (24) in 88% yield.[22] Similarly, oxidation of hexaethylbenzene (25) gives hexaethyl-2,4-cyclohexadienone (26) in good yield. There was no noticeable epoxidation of the resulting dienones because only a limited amount of oxidant was used and probably because of the lower reactivity of conjugated systems.[23,31] The structures of dienones (24) and (26) were deduced from their spectral properties and reactions. The dienones are quite stable with respect to dimerization which is in direct contrast with the behavior of less substituted dienones.[24] Maleic anhydride and ethyl azodicarboxylate react with (24) under mild conditions to form adducts (27) and (28), but (26) does not react at all.



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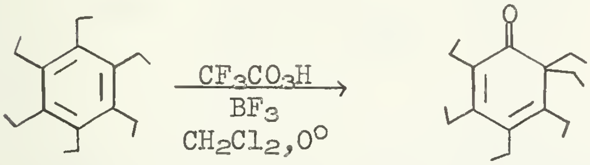
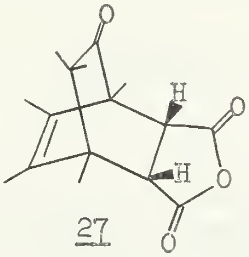


25 26



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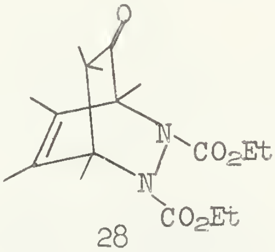

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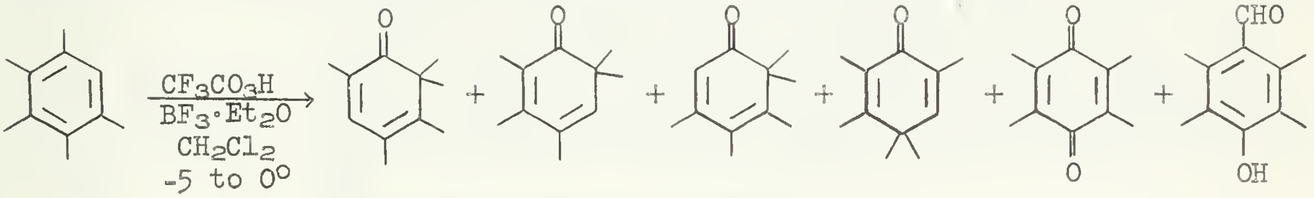
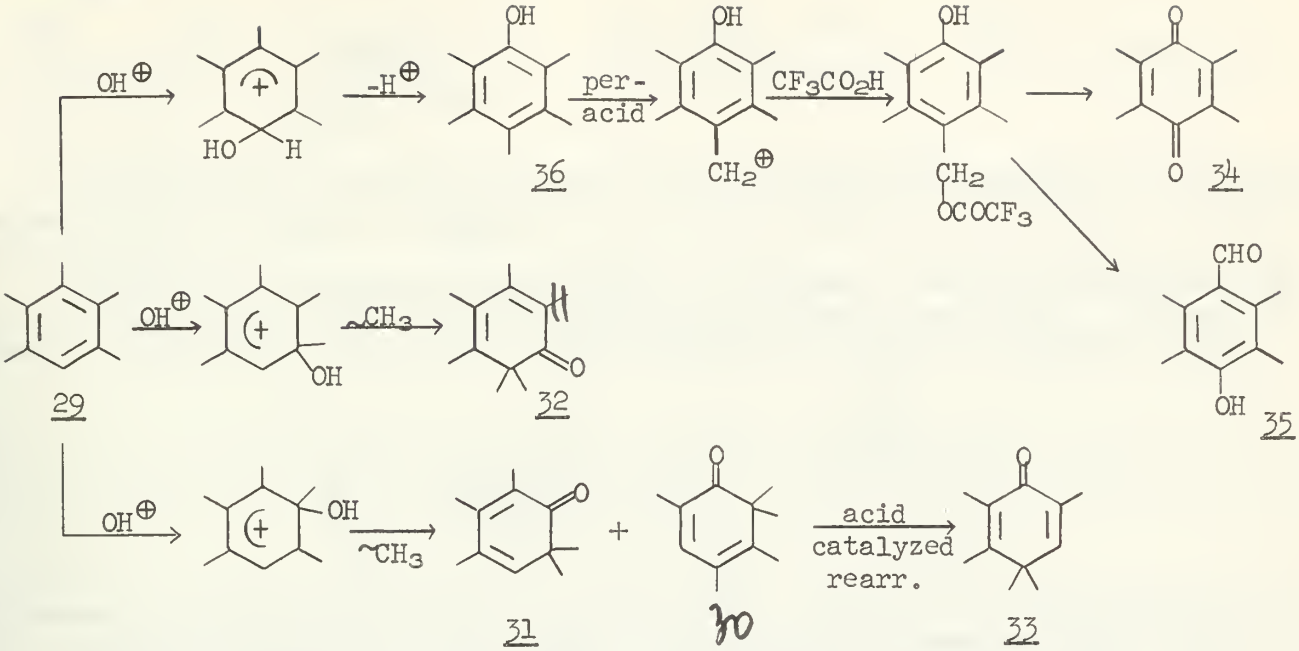
The oxidation (75% conversion) of pentamethylbenzene (29) with peroxytrifluoroacetic acid - boron fluoride etherate affords six products.[25] The two major components are 2,4,5,6,6-pentamethyl-2,4-cyclohexadienone (30) and the 2,3,4,6,6-pentamethyl isomer (31). A 7% yield of 3,4,5,6,6-pentamethyl-2,4-cyclohexadienone (32) was obtained, but no 2,3,5,6,6-pentamethyl-2,4-cyclohexadienone was detected. The three other products identified were dienone (33), duroquinone (34), and p-hydroxytetramethylbenzaldehyde (35). A plausible mechanistic pathway to these products involves the initial attack of $OH^{\oplus}$ on the aromatic nucleus as shown on the following page in Scheme 5.

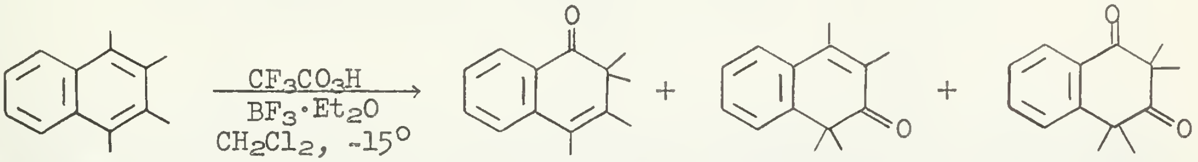


29 30(33%) 31(37%) 32(7%) 33(7%) 34(7%) 35(7%)

Scheme 5

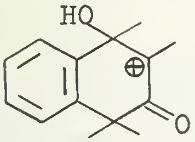


1,2,3,4-Tetramethylnaphthalene (37) was oxidized at -16 to -12° with a 10% excess of peroxytrifluoroacetic acid - boron fluoride etherate in methylene chloride.[26] Three products were obtained: 2,2,3,4-tetramethyl-1(2H)-naphthalenone (38), 1,1,3,4-tetramethyl-2(1H)-naphthalenone (39), and 2,2,4,4-tetramethyl-1,3-dioxotetralin (40).



37 38(61%) 39(21%) 40(18%)

Products (38) and (39) are formed by processes described previously. Dioxotetralin (40) is found to be formed by oxidation of (38) and not by oxidation of (39). When (38) is oxidized with peroxytrifluoroacetic acid - boron fluoride etherate at -15° almost quantitative conversion to (40) is observed. Similar oxidation of (39) would require the intermediacy of (41) which is expected to be destabilized because of the necessity of placing a positive charge on a carbon atom alpha to a carbonyl. Consequently, oxidation of (37) with a large excess of oxidant at -10° gave no naphthalenone (38); however, (39) and (40) were formed in 54 and 40% yields, respectively. It follows then that (40) is formed directly from oxidation of (38).



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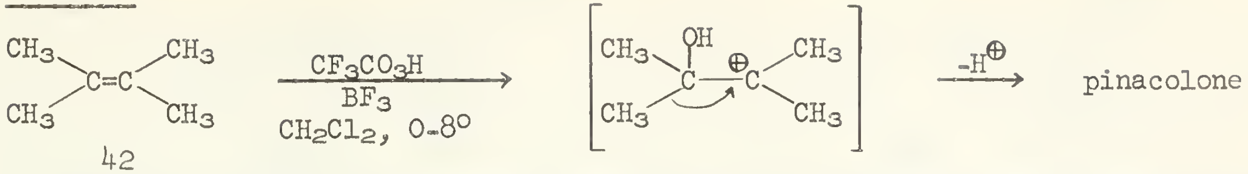
OXIDATION OF ALKENES TO KETONES

Since, as previously stated, epoxidation of olefins by organic peracids is believed to proceed through attack of positive hydroxyl,[1] and boron fluoride is known to catalyze ring opening of epoxides to carbonyl compounds via a Wagner-Meerwein rearrangement,[27] Hart and co-workers[28] reasoned that they could probably effect the same overall reaction in one step by using peroxytrifluoroacetic acid - boron fluoride. Oxidation of 2,3-dimethyl-2-butene (42) with peroxytrifluoroacetic acid - boron fluoride in methylene chloride at 0-8° gives pinacolone in 75% yield. The omission of boron fluoride reduces the yield of pinacolone to 16%. Following his previous arguments, Hart proposed a mechanism which involves initial attack by positive hydroxyl or some complexed form of it on the olefinic double bond followed by methyl migration and loss of H⊕ to afford pinacolone as depicted in Scheme 6.

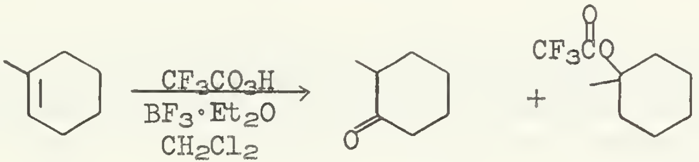
Scheme 6



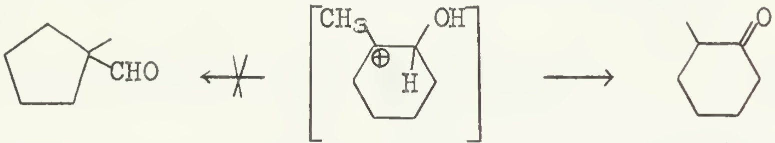
42

The oxidation of 2-methyl-2-butene gives only 3-methyl-2-butanone. In addition, oxidation of either cis- or trans-3-methyl-2-pentene gives only 3-methyl-2-pentanone in good yield.

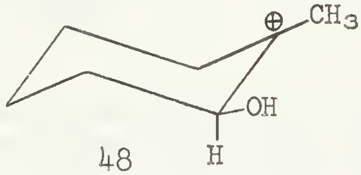
Oxidation of 1-methylcyclohexene (43) at 0° affords 2-methylcyclohexanone (44) and a non-oxidation product, 1-methylcyclohexyltrifluoroacetate (45), in 8 and 15% yields, respectively. The yield of (44) increases to 41% and the yield of (45) decreases to 9% when the oxidation is run at 40°. Addition of trifluoroacetic acid to 1-methylcyclohexene gives only (45). The oxidation intermediate (46) could give (44) by hydride migration, or 1-methylcyclopentanecarboxaldehyde (47) by ring contraction. However, no aldehyde is formed in the reaction. Of the two carbonium ion intermediates, both could lead to ring contraction product, but only the carbonium ion with the hydroxyl in the equatorial position could lead to hydride migration and ultimate formation of (44).



43 44 45



47 46 44



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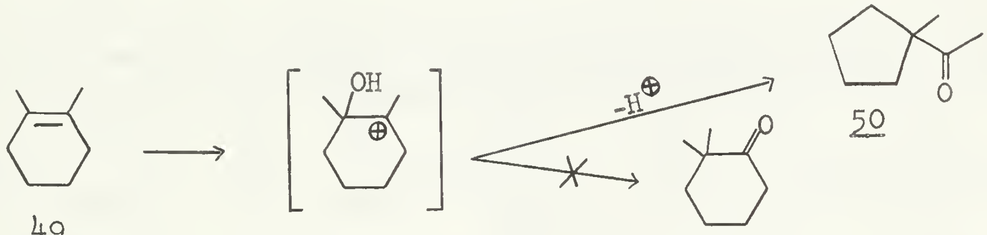
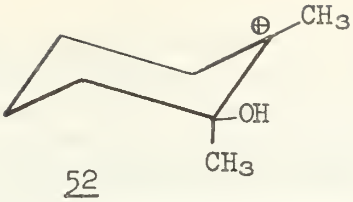
The oxidation of 1,2-dimethylcyclohexene (49), on the other hand, gives only 1-acetyl-1-methylcyclopentane (50), the ring contraction product. No 2,2-dimethylcyclohexanone (51) was detected in the reaction product. See Scheme 7. Considering the two possible intermediate carbonium ions, (52) and (53), one can see that only (52) can lead to (51) by methyl migration. Bunton and Carr[29] suggest that (53) should be the most stable carbonium ion on the basis of stabilization of the positive charge by participation of the hydroxyl group.

Scheme 7



49 50 51



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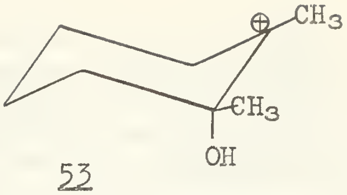

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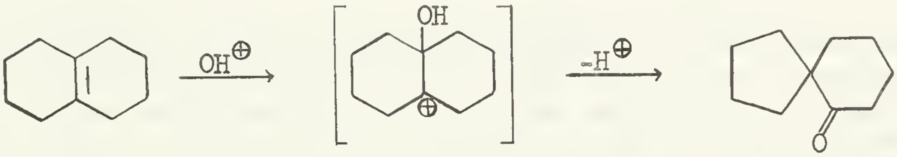
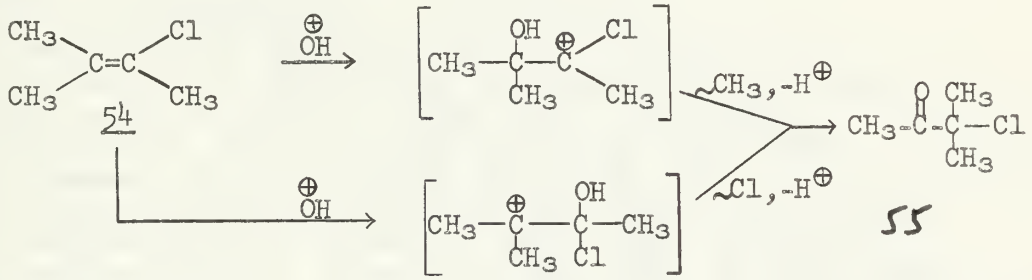
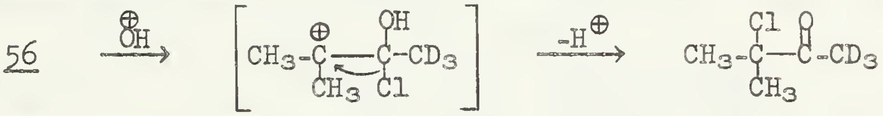
Oxidation of $\Delta^{9,10}$-octalin gives an 86% yield of the same spiro ketone as that observed in the pinacol rearrangement of the corresponding trans-glycol.[30]



The oxidation of 3-chloro-2-methyl-2-butene (54) gives only 3-chloro-2-methyl-2-butanone (55) and, as depicted in Scheme 8, this product could result from either of two possible intermediates, one in which methyl migrates and one in which chlorine migrates. 2-Chloro-3-methyl-2-butene-1,1,1-d_3 (56) was synthesized and subsequently oxidized to determine which of the two mechanisms was operative. The product obtained gave a singlet absorption in the nmr at τ 8.36 corresponding to product (57); therefore, chlorine migration had taken place in preference to methyl migration.

Scheme 8





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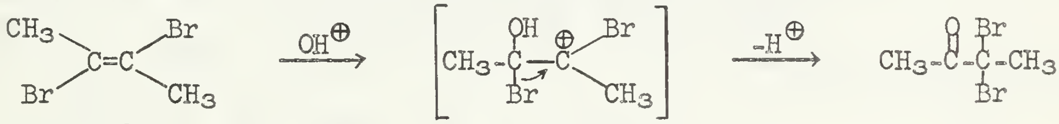
To determine the preference between methyl and bromine migration, 2,3-dibromo-2-butene (58) was synthesized and then oxidized to give only one product, 3,3-dibromo-2-butanone (59), which must have arisen from bromine migration.



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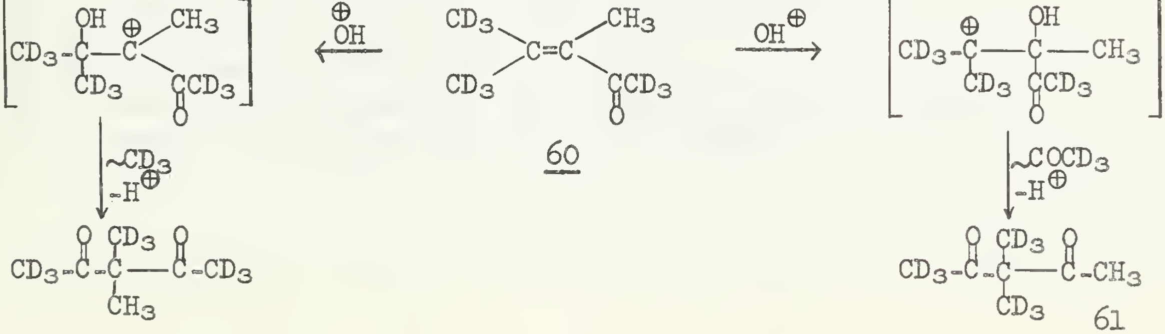
The preference between methyl and acyl migration was studied by examining the product obtained from the oxidation of 4-methyl-d_3-3-methyl-3-penten-2-one-1,1,1,5,5,5-d_6 (60). The resulting deuterated diketone product obtained from the oxidation of (60)



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had only a single peak in the nmr at τ 7.93 and was assigned structure (61). Methyl migration would have resulted in the formation of a diketone with an expected singlet in the nmr at about τ 8.7. Therefore, acyl migration must have taken place. Another example of acyl migration has been observed by House[32,33] in the acid catalyzed rearrangement of 1,3-diphenyl-2,3-epoxy-1-propanone-2-C^{14} to 2,3-diphenyl-1,3-propanedione-1-C^{14}.

CONCLUSION

Peroxytrifluoroacetic acid - boron fluoride has been shown to be a strong oxidant used under mild conditions to effect specific changes in aromatic and olefinic systems. The reactions are most readily explained by postulating cationic hydroxyl or some complexed form of it as the attacking species. The oxidations of aromatic compounds provide, in many cases, an easy route to otherwise difficulty synthesized compounds while the oxidations of substituted olefins allows one to examine conformational preferences in carbonium ions and to study migratory aptitudes of various substituents in the course of rearrangements initiated by the oxidation.

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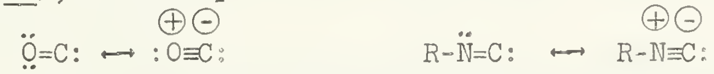
THE CHEMISTRY OF NUCLEOPHILIC CARBENES

Reported by D. R. Brittelli

January 4, 1968

INTRODUCTION

Although ordinary carbenes exhibit a strongly electrophilic character,[1] the introduction of an electron-rich α hetero atom (specifically N, O, S, or Se) into the structure produces gross changes in the reactive nature of such latter molecules, so that they are instead markedly nucleophilic. The altered electronic character expressed in the additional resonance contributors 1b and 2b provides a rationale for the nucleophilic properties of the stable "carbenes" carbon monoxide (1a) and the isonitriles (2a), for example.



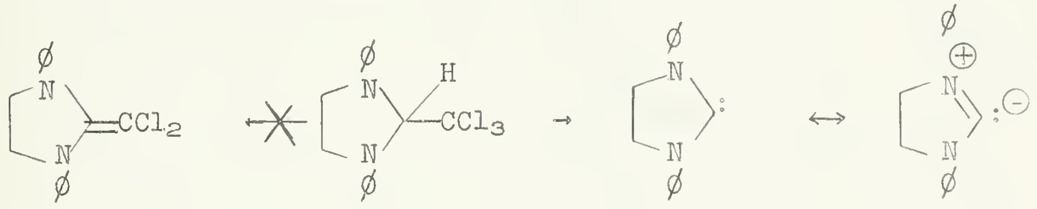
$$\ddot{\underset{..}{O}}{=}C: \longleftrightarrow :\overset{\oplus\ominus}{O{\equiv}C}: \qquad R{-}\ddot{N}{=}C: \longleftrightarrow R{-}\overset{\oplus\ominus}{N{\equiv}C}:$$

1a 1b 2a 2b

This seminar will be concerned with the chemistry of certain "nucleophilic carbenes" di-α-substituted with two of the above enumerated hetero atoms. The misnomer "nucleophilic carbene" will be used in referring to these molecules in order to be consistent with the terminology established in the literature, although the terms "betaine" and "ylide" are more accurate descriptions.

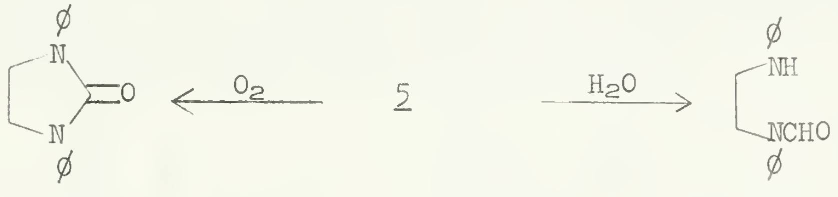
THE CHEMISTRY OF "1,3-DIPHENYL-2-IMIDAZOLIDINYLIDENE"

In 1960, Wanzlick and Schikora, attempting to synthesize the dichloro ethylene 3 by the elimination of the elements of HCl from the trichloromethyl imidazolidine derivative 4, instead found themselves confronted with a colorless crystalline material 5, which behaved chemically like 5ab.[2]



3 4 5a 5b

Reaction with atmospheric oxygen gave an intense purple solution from which could be isolated the colorless 1,3-diphenyl-2-imidazolidone (6) in 90% yield, and reaction with water gave a 99% yield of the monoformyl derivative of dianilinoethane (7).



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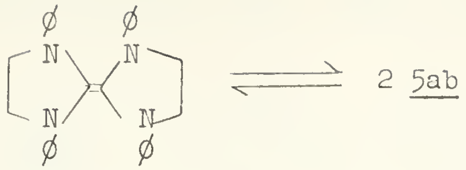
The strongly nucleophilic properties of 5 led to the extensive investigation of this material and the subsequent generation of the field of nucleophilic carbene chemistry, and in fact the reactions of 5 were initially invoked as good evidence for the existence of 5ab. Further investigations of 5 showed it to be the dimer, below.[3] Its chemistry was explained as its being a source of the ylide-carbene, and an equilibrium between the dimer and two moles of the carbene was proposed.

That the molecule 5 was indeed the dimer formulated was shown by the appearance in the Raman spectrum of a strong carbon-carbon double bond stretching absorption at 1640 cm^{-1}, absent in the infrared. Molecular weight determinations in camphor at 170° (for which concentration of solutes the molal freezing point depression



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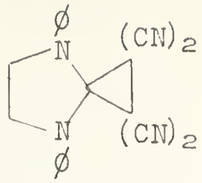

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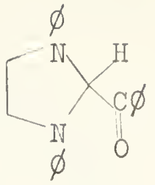

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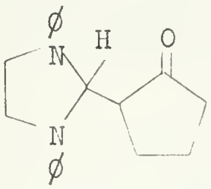
constant of 39.7 is valid) showed molecular weights of 316, 293, and 306; calculated for 5, 444.6. This was taken as an indication that at this temperature the dimer is about half dissociated.[3]

Further synthetic work in the form of the facile high-yield (92%) preparation of 5 from triethyl orthoformate and dianilinoethane lent additional credence to the existence of the carbene.[4,5] A whole new series of reactions designed to test the existence of the carbene were also initiated. While electrophilic carbenes are very reactive toward ordinary olefins (2-butene and cyclohexene, for example), 5 (presumably 5ab) was observed to undergo reaction only with the extremely electron-deficient TCNE to give cyclopropane 8; reaction with aryl aldehydes gave compounds arising formally from the insertion of the "carbene" into the carbonyl carbon-hydrogen bond, 9,[3] along with traces of the corresponding benzoins derived from the aromatic aldehydes.[6,7] This provided convincing evidence for the ylide nature of the carbene, which here was serving in the role of cyanide as a catalyst for this latter side reaction.

Other reactions included "insertions" into the α-hydrogens of cyclopentanone, 10, nitromethane, 11, and a whole host of other "C-H acidic compounds."[6,8,9]



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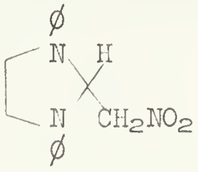

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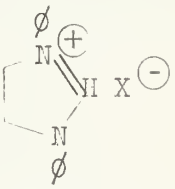

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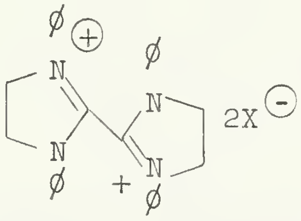
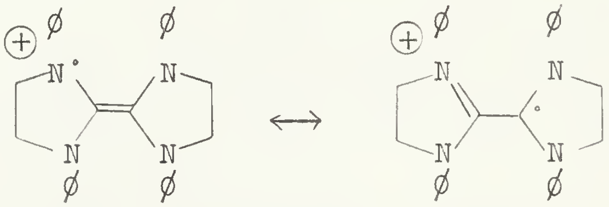
Lemal and Kawano contributed more circumstantial evidence in the synthesis of 5 in quantitative yield through the action of the hindered bases mesityl magnesium bromide or sodium triphenyl methoxide on imidazolium salts 12 ($X=ClO_4$).[10] The reaction was in fact found to be reversible, as 5 and non-aqueous acid regenerated 12 in quantitative yield.[11] This latter work also brought out the strong electron-donating properties of 5, in that this material, brought into reaction with iodine immediately precipitated the diiodide 13a, with bromine the dibromide 13b, and with silver nitrate metallic silver and the dinitrate 13c.



13a, X=I
13b, X=Br
13c, $X=NO_3$



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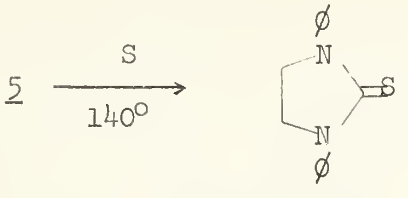
In addition, it was found that a mixture of equimolar quantities of 13 and 5 disproportionated to two moles of the purple cation radical 14, identified by esr, the same radical which results from the reaction with oxygen. In spite of these hints of the real character of 5, the chemistry of 5 was still rationalized as its

being a source of carbene-ylide 5ab. Further transformations discussed included reaction with molecular sulfur, ethyl chlorocarbonate, and diazo compounds.



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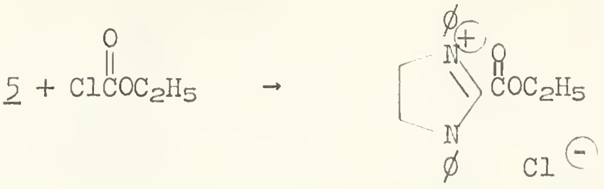

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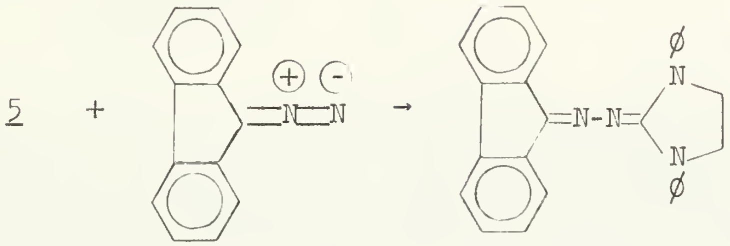

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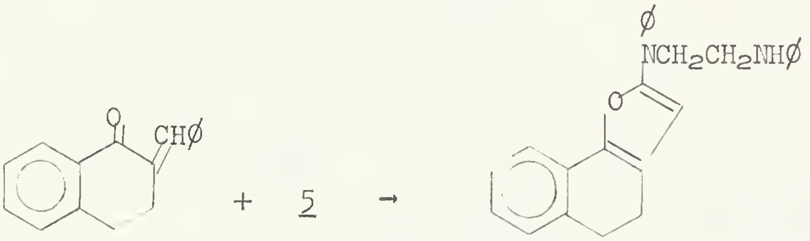
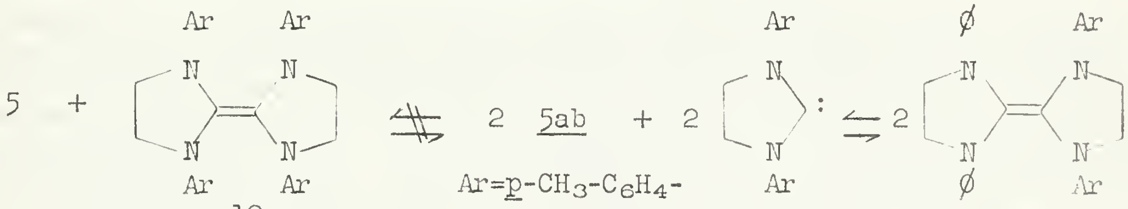
Although the reaction with sulfur has some analogy in the chemistry of electrophilic carbenes,[1,12] strongly electrophilic carbenes are known to react with diazo compounds with the loss of a molecule of nitrogen to give olefins. Thus, the production of azine 17 was taken to be still another illustration of the difference between the chemistry of nucleophilic and electrophilic carbenes.[13] The nucleophilicity of the carbene also suggested that it should react with the electrophilic double bond of α,β-unsaturated ketones in a Michael-type addition. Reaction did take place, but in a rather surprising manner.[6]



The question of the equilibrium 5 $\rightleftharpoons$ 2 5ab was finally answered when Lemal, Lovald, and Kawano found that 5 and the tetra-p-tolyl analogue 19 did not give any cross-product dimer after heating a mixture of the two dimers in xylene at reflux for two hours.[14]



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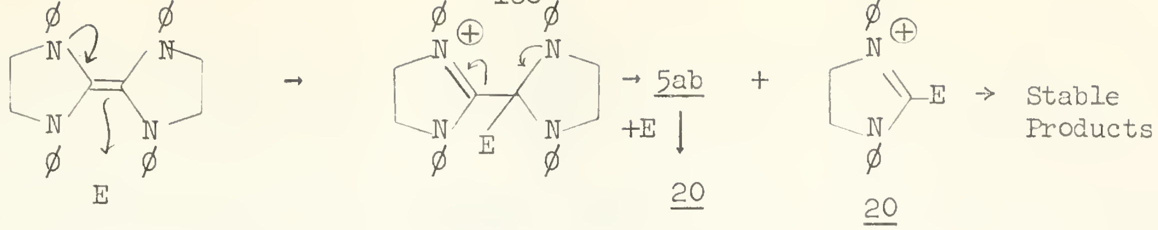
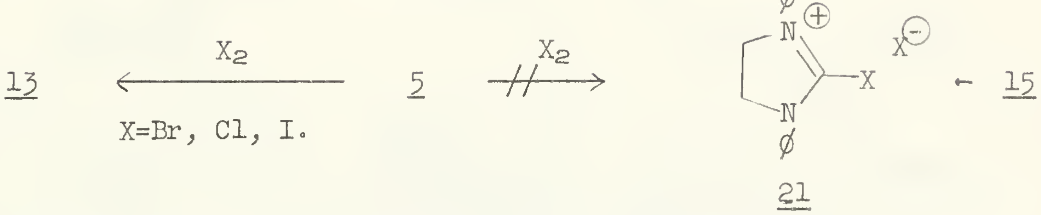
The reactions of 5 were then rationalized by these workers as those of an eneamine, and a new mechanistic scheme was proposed (Scheme I). In addition, Wanzlick, Esser, and Kleiner measured the molecular weight of 5 in pyridine at room temperature and found it to be not detectibly dissociated.[5] In fact, the great significance of the halogen reactions was finally appreciated; while 21 was the product expected from reaction with the carbene, only the salts 13 could be isolated. The anticipated product 21 was independently synthesized from thione 15 by reaction with phosgene. It was found that this material readily reacted with water to produce imidazolidone 6.



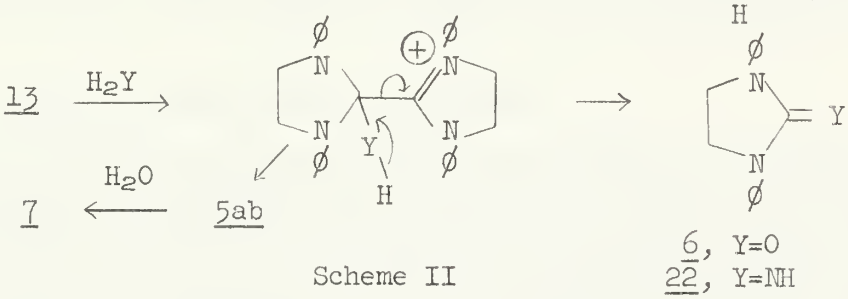
Scheme I



No such products could be detected from the halogen reactions.[11]

It is important to note, however, that in the proposed mechanism, half of the product is derived from the eneamine reaction of the dimer and half still from the "carbene." Considerable evidence has been found for this mechanism and the intermediacy of the carbene by the examination of the products from the hydrolysis of the salts 13 with water or aqueous ammonia; equal amounts of two structurally different types of materials are isolated.[10,11] The results of these reactions are tabulated and the explanation formulated in Scheme II. Thus, it appears that the carbene is indeed capable of transient existence. No more attempts were made to characterize it, however, as the effort in the field became directed toward the chemistry of benzothiazolium compounds.

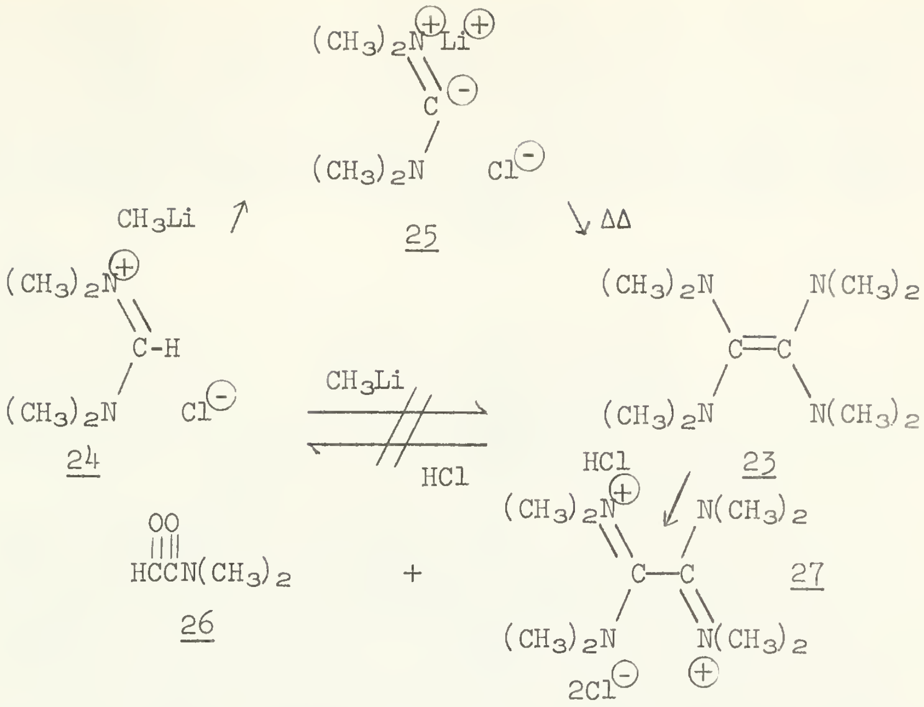
Reactant	Carbene Product	Dimer Product
Water	77% (7)	78% (6)
Aqueous Ammonia	48% (7)	49%, 7% Y=0 (6) 42% Y=N (22)



Scheme II

THE CHEMISTRY OF TETRAKIS-(DIMETHYLAMINO)-ETHYLENE

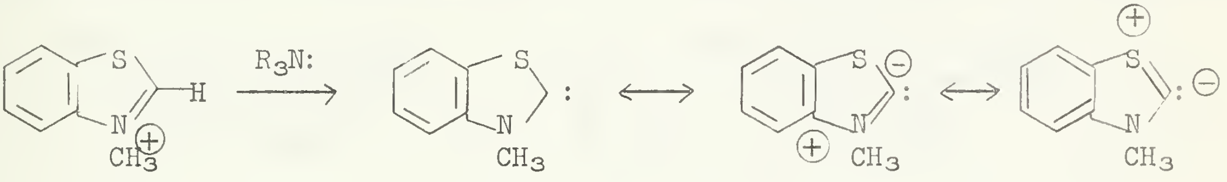
Although tetrakis-(dimethylamino)-ethylene (TDAE), 23, was first synthesized many years before the nucleophilic carbene question was raised,[15] its unusual properties were not further investigated until Wiberg and Buchler took up the problem at a time contemporaneous with the Wanzlick group's work on the bis-(1,3-diphenyl-2-imidazolidinylidene) series. Although initial work was concerned with the strong electron-donating properties of TDAE (the compound is a "quasi-metal" with reducing properties intermediate between those of zinc and copper),[16,17] analogies to the chemistry of 5 were soon sought. While 5 reacted with acids to give the salts 12 which could be reconverted to 5 with strong bases, no analogous scheme held in the TDAE series. Reaction of formamidinium salt 24 with methyl lithium yielded a stable lithium salt 25 which upon pyrolysis gave TDAE in 2% overall yield.[18] The reverse reaction of TDAE with acids gave only a messy mixture of compounds from which could be isolated the octamethyl oxamidinium salt 27 (22%) and the dimethyl amide of glyoxylic acid (26, 47%), no trace of the expected tetramethylformamidinium salts being obtained.[19]



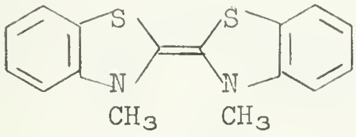
Thus, there was no real question of the possibility of the existence of the nucleophilic carbene in this series. This appears to be due to the inability of the π-electron system to achieve co-planarity. Calculations have in fact predicted that the methyl groups should be twisted at an angle of 50 degrees from the plane of the carbon-carbon double bond.[20] The only indication for the possible existence of the carbene is the production of TDAE from the heating of tris-(dimethylamino)-methane,[21] a reaction that can easily be rationalized without the necessity of invoking the carbene, however.

THE CHEMISTRY OF 3-METHYL-2-BENZOTHIAZOLIDINYLIDENE

The tentative success achieved by Wanzlick and Schikora in the imidazolidinylidene series prompted them to try to design and synthesize a stable nucleophilic carbene. Wanzlick suggested that this might be most likely if the carbene could achieve "quasi-aromatic resonance stabilization."[22] Soon after this goal was announced, Wanzlick and Kleiner described the stable carbene 3-methyl-2-benzothiazolidinylidene (29abc), produced by the reaction of tertiary amines with benzothiazolium salts 28.[23]



28 29a 29b 29c



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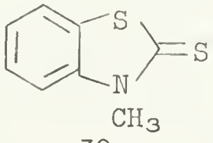

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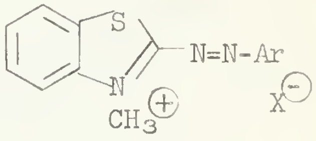

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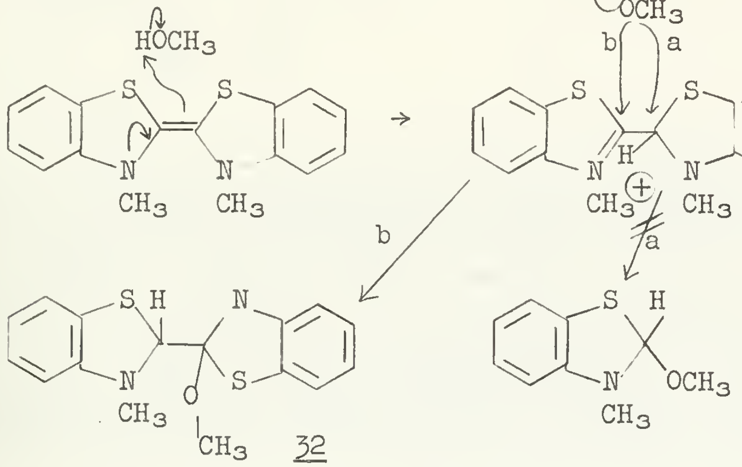
It was later found that this material was also a dimer, 29, although the relative geometry about the double bond is still unknown.[24] The dimer also showed reactions characteristic of the "half-molecule" 29abc. Reaction with molten sulfur or with powdered sulfur in benzene at reflux led to the thione 30, acids regenerated benzothiazolium salts 28, and the reaction with diazonium compounds gave the azodyes 31.[23]

Metzger and co-workers meanwhile found a whole series of reactions supporting

the carbene-dimer equilibrium in this series.[24] These were similar to those found for the imidazolidinylidene, but there were some divergences. The reactions with TCNE, halogens, "C-H acidic compounds" and aryl aldehydes went analogously, even to the point of there being benzoins formed in the latter reaction. However, the carbon-carbon double bond was somewhat less subject to fission here and in the case of the addition of methanol, the initial addition complex went to a stable product 32 containing the dimer skeleton complete instead of splitting into the monomeric units.



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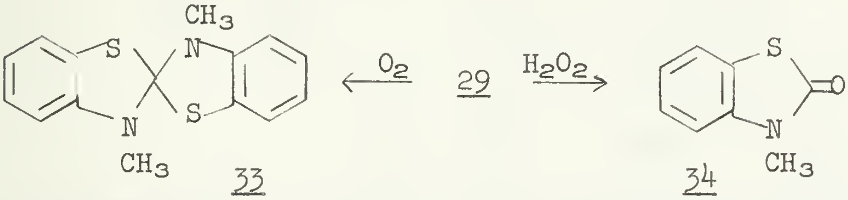
Another anomaly was the reaction with oxygen; spirane 33 was produced instead of the anticipated benzothiazolidinone 34, which did, however, arise from the reaction with hydrogen peroxide.



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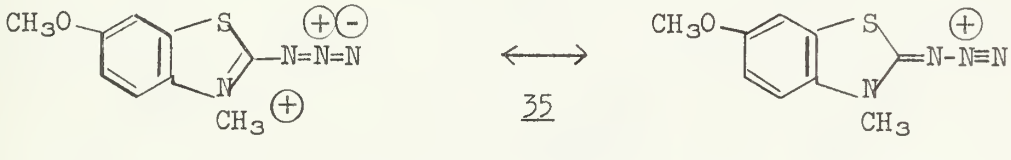
While it may appear that these results were going to parallel those of the imidazolidinylidene compounds, especially in regard to the negative conclusion about the existence of any equilibrium, the existence of the carbene itself was put on a firm basis by the differentiation of its reactions from those of the dimer by Quast and Hünig, who succeeded in this endeavor by the use of the strongly electrophilic azidinium salts 35 as trapping reagents.[26] For example, 29 brought into reaction with



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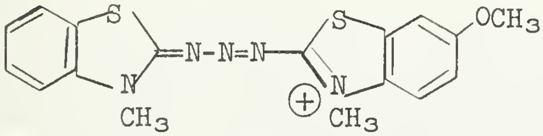

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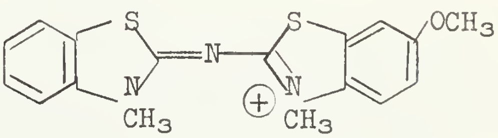

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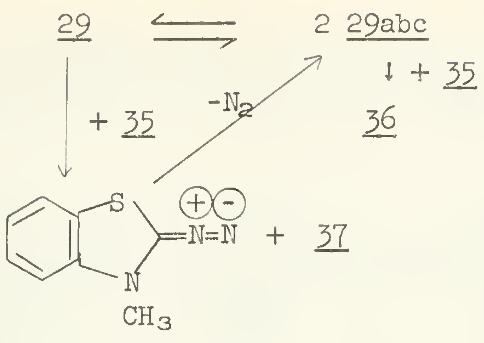
35 produced 14% of the triazo compound 36 and 50% of the monoazo 37. In marked contrast, the only product isolated when 29abc was generated *in situ* from 28 and triethyl amine was 36. With weaker electrophilic azides, for example 38, only compounds with one bridging nitrogen were isolated under either set of conditions (carbene generated *in situ* or by reaction with the dimer).[27] The explanation for these reactions is depicted in Scheme III.

Scheme III



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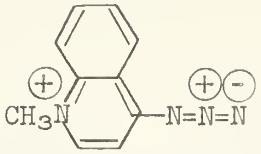

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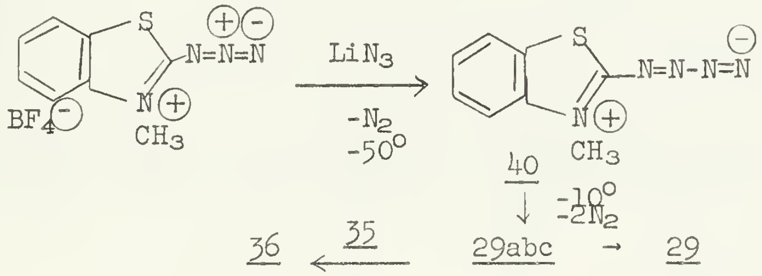
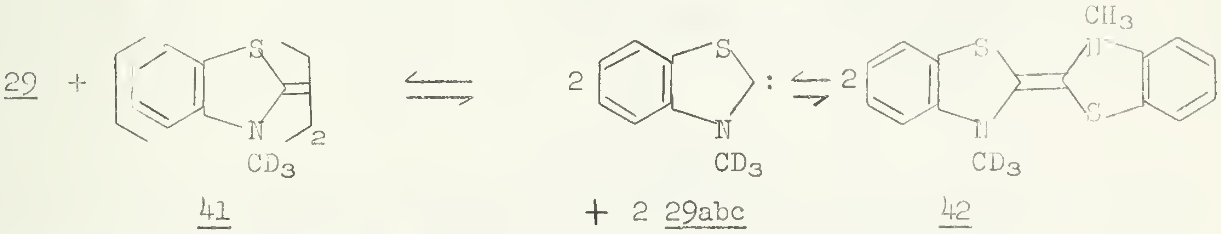
Reaction with the dimer gave the diazo benzothiazolidine 39 and the monoazo compound. The former decomposed with loss of nitrogen to yield the carbene, which in turn coupled with the salt 35 to produce the triazo compound. This same product could be produced independently by reaction from the dissociated carbene.

This work was reinforced by H. Balli's description of the controlled decomposition of the "aza-homologous" diazo compound 40 in the presence of different trapping reagents, for example the above azidinium salts. In the absence of such strong electrophiles, the dimer was isolated.[28] Finally, the existence of the carbene-dimer equilibrium was strengthened in this series in the crossing experiment of



J. -J. Vorsanger.[29] A mixture of 29 and the dideuteriomethyl derivative 41, after crystallization from a benzene solution in which they had been allowed to equilibrate for six hours at room temperature showed a peak at m/e 301 due to the hybrid dimer 42, absent in the spectra of both starting materials. Thus it appears that the equilibrium here is real and that the carbene may exist in solution.[29]

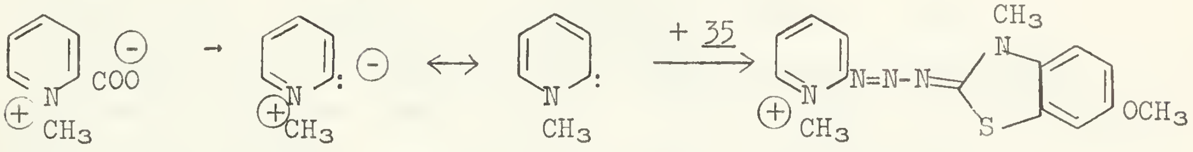


EVIDENCE IN OTHER SYSTEMS

The success of nucleophilic carbene chemistry described above led to the expansion of the field into many wide-spread areas. Quast and Frankenfeld found that nucleophilic carbenes were produced from heterocyclic N-methyl betaines by an extremely facile decarboxylation at 40-80°; the intermediate carbene could be trapped by the now standard method. One example is illustrated in the pyridine compound 43.[30]

Other evidence for nucleophilic carbenes comes in the form of the facile exchange of the 2-proton of numerous five-membered ring aromatic heterocycles with 1,3-heteroatoms.[31-36] Interestingly, the C_{13}-H coupling constant has been determined for thiazolium and oxazolium compounds 44 and 45 and found to be 218 and 247 Hertz, respectively, interpreted to show the equivalent of sp hybridization on the 2-carbon.[32]

However, the correlation of the magnitude of the C_{13}-H coupling constant with the amount of s-character at C^{13} has been shown by Karabatsos and Orzech to be "meaningless when two or more heteroatoms are bonded to C^{13}."[37]



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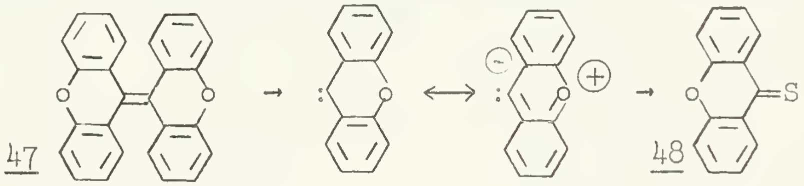
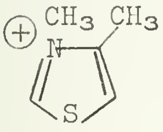
One last piece of evidence is the decomposition of the tetrazolium salt 46 to nitrogen and diethyl carbodiimide at high pH, by removal of the 2-proton and the slow decomposition of the resulting ylide-carbene (deuterium exchange is possible at lower concentrations of base).[32]

CONCLUSION

The work on which rests the basis of nucleophilic carbene chemistry has been related above. Much of the value of this work lies in the aid it lends to the understanding of many seemingly anomalous reactions in the literature. Indeed, a review of these has been made by Wanzlick.[22] The biochemistry of thiamine (which contains a thiazolium ring),[34] the Butlerow reaction (the base-catalyzed condensation of formaldehyde to form sugars), and the production of benzoic acid by the fusion of chlorobenzene or sodium benzenesulfonate with sodium formate have all been seen more clearly in invoking the intermediacy of a nucleophilic carbene. Other examples are the reaction of bixanthylene (47) with sulfur to give thione 48[13] and the oxidative coupling of benzanthrone.[38] Thus it is seen that nucleophilic carbene chemistry has been useful in broadening the basic concepts of organic chemistry in that it has enhanced the understanding of otherwise difficultly rationalized reactions.





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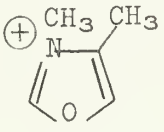

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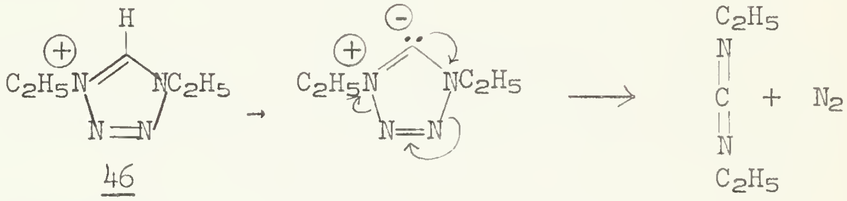

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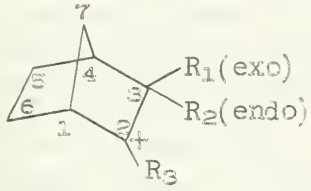
THE STEREOCHEMISTRY OF 3,2 SHIFTS IN NORBORNYL CATIONS

Reported by Judy Pei-yin Soong January 8, 1968

INTRODUCTION

A vexing problem in norbornane chemistry has been in understanding the remarkable stereospecificity of the 3,2 shifts in structure 1. These processes involve the migration of a 3-exo in preference to a 3-endo substituent to a 2-cation, despite the apparent symmetry about the C_2-C_3 bond. The stereospecificity is observed in the 3,2-hydride shift, the 3,2-methyl shift and the pinacol rearrangement in the norbornyl system. This seminar will describe experimental evidence for this stereospecificity and different mechanisms proposed to explain it.



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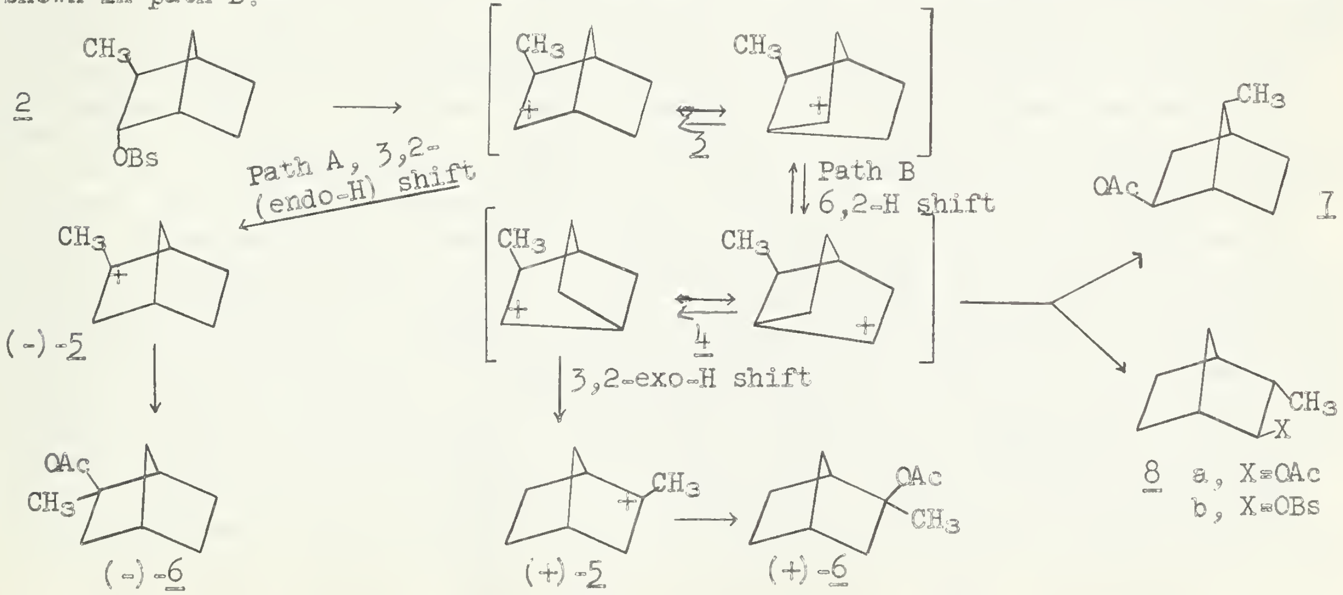
THE 3,2 HYDRIDE SHIFT IN NORBORNYL CATIONS

The distribution of ^{14}C in the solvolysis products of exo-norbornyl-2,3-$^{14}C_2$ p-bromobenzenesulfonate[1] in formic acid reported by Roberts et al., was explained by Dills,[2,3] who introduced the 3,2-hydride shift in addition to Roberts' 6,2 hydride shift and bridged carbonium ion. Recently nmr studies[4,5] have shed further light on the 3,2 hydride shift that attends the formation of 2-norbornyl cations. The nmr spectrum of the 2-norbornyl cation, as its SbF_6^- salt, undergoes significant changes with varying temperature. At -120°C, 2-exo-norbornyl fluoride in mixed SbF_5-SO_2-SO_2F_2 solvent, consists of three peaks at -321 cps(area 4), -189 cps(area 1) and -132 cps(area 6) from external tetramethylsilane (at 60 Mc.). No important change appears up to -60°C, but at higher temperatures the peaks broaden, and coalesce near -23°C into a single peak, which sharpens to 20 cps half-width at 3°C. The high temperature spectrum is interpreted to indicate time-average equivalence of all protons in the 2-norbornyl cation in nmr scale. Such equivalence is possible only if the Wagner-Meerwein rearrangement, the 6,2 hydride shift, and the 3,2 hydride shift are occurring rapidly and simultaneously. The low-temperature spectrum is postulated to result from a diminished rate for the 3,2 hydride shift. The rates of 3,2 shift have been determined from the temperature dependence of spectrum at a series of temperatures, and it appears to be the slowest of the three rearrangement processes in norbornyl system.

Berson and coworkers[6,7] reported that the solvolysis of (+)-3-exo-methyl-2-endo-norbornyl p-bromobenzenesulfonate 2 in acetic acid-sodium acetate at 100°C gave a mixture of acetates. Instead of invoking a 3,2-endo shift[8] (path A in scheme I), an alternative mechanism involving an exo-vicinal 3,2 hydride shift was proposed as shown in path B:

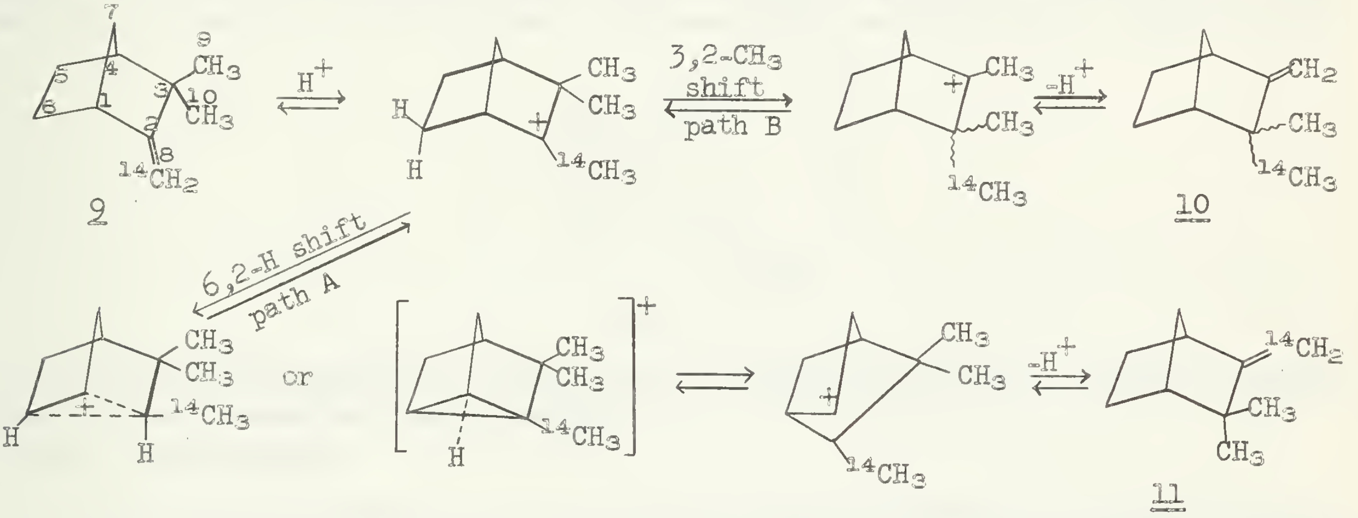


The mechanisms are clearly distinguishable in the optically active series once the relative configurations of the starting material and products are established.

Compound 6 constitutes only 3.5% of the acetate products. The sign and magnitude of rotation set a minimum selectivity of 90% in favor of path B over path A. Compound 8a resulting from 4 is formed with 102% retention of optical purity. Further the product ratios 6:8a and 6:7, 0.247 and 0.233, respectively, measure the proportion of the secondary ion 4 undergoing hydride shift and solvent capture. The agreement of these values with those found[9] in the acetolysis of 8b (0.242, 0.229), excludes any appreciable contribution of direct formation of tertiary cation 5 from cation 3 via path A, since such a process would have caused the ratio of 6:8a and 6:7 to be greater from 2 than from 8b. The ratio suggests that at most 2% of the tertiary acetate comes from cation (-)-5. This leads to a ratio of exo-shift/endo-shift of at least 100.

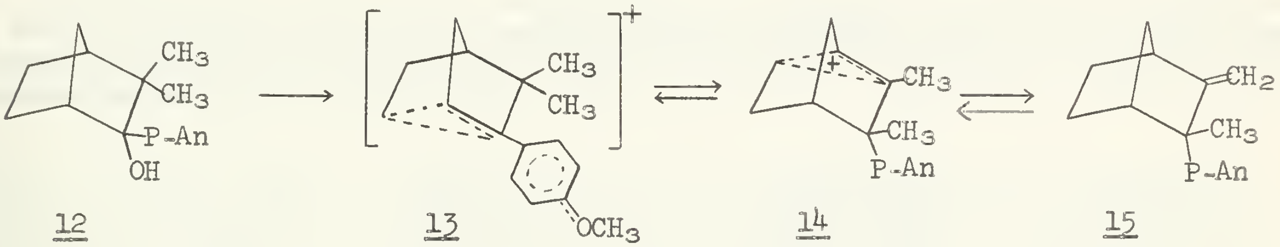
3,2 METHYL SHIFT IN NORBORNYL CATIONS

In all reported cases, when direct competition between exo,exo and endo,endo 3,2 shifts are possible, the former have always found to predominate;[10-15] the occurrence of this rearrangement in the camphene series is particularly interesting. In 1953, two independent tracer studies[13,14] of the camphene-8-^{14}C 9 racemization process demonstrated the operation of a methyl shift and a 6,2 hydride shift process in the course of racemization under a variety of conditions. The ratio of the two pathways is both temperature and solvent dependent. The proposed mechanisms are shown in scheme II. Path A and Path B may be experimentally distinguished by ^{14}C-distributions resulting from the operation of each starting with labeled camphene 9. In path A, no change in the ^{14}C-distribution occurs as in compound 11, while in path B, the ^{14}C becomes distributed among the side chain carbon atoms as in compound 10. Ozonative degradation (formaldehyde isolated as dimethone derivative) can at best determine total ^{14}C at C_8, but the information as to the relative involvement of endo and exo methyl migration cannot be estimated. Vaughan and coworkers[10] introduced ^{14}C at C_{10} in camphene and determined the change in radioactivity at the methylene carbon. They estimated from their own data and that of Roberts and Yancey[13] the extent of racemization of camphene by the three different routes, 3,2-exo-methyl shift, 3,2-endo-methyl shift and 6,2 hydride shift, under the influence of pyruvic acid in acetonitrile, and came to the proportions 58-68%, 22-12% and 20% respectively of total racemization. Hirsjarvi et al.[12] repeated the experiments of Roberts and Yancey with optically active camphene employing pyruvic acid as catalyst, they found that tricyclene is formed (1-6%) both with and without acetonitrile as solvent. If camphene labeled at C_8 undergoes racemization either by an endo-methyl or by an exo-methyl shift, the rate of change of the radioactivity at C_8 must be equal to the rate of conversion of (-)-camphene to (+)-camphene. The experimental data showed that the former change was 22% and the latter degree of conversion 20.6%, which are practically equal. An exo-methyl shift in camphene labeled at C_{10} should lead to the same result whereas an endo-methyl shift should not lead to an increase in the

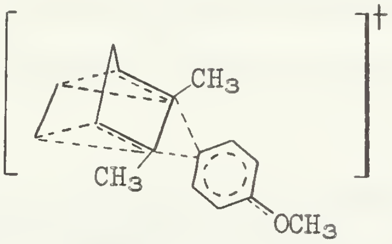


radioactivity at C_8. Experimental results showed that during the period the radioactivity change was 20.3 ± 4%, and 21.3% of the (+)-camphene was converted into (-)-camphene. Hence they concluded that the racemization had taken place almost exclusively via an exo-methyl shift. The formation of tricyclene offers an explanation for the observed distribution of ^{14}C radioactivity among C_8, C_9 and C_{10}.

The dehydration of p-anisylcamphenilol[15,16] 12 provides another striking example of this type of reaction. The olefin 15 formed from optically active 12 in formic acid is optically active. It presumably arises from the cation 14, which is the product of a 3,2-exo-methyl shift in the p-anisylcamphenilyl cation 13. Although the degree of retention of optical purity is unknown, the product olefin has a substantial activity, and since a shift of the p-anisyl group would convert cation 14 to its mirror image, little, if any, of the cation is diverted in this direction. This is despite that fact that a p-anisyl group is generally far superior to a methyl group in the ability to stabilize positive charge at a β-carbon; the multiple bridge cation 16, clearly, is not involved. It seems highly probable that if endo-p-anisyl is prohibited from migrating in this case, then endo-methyl in the camphene racemization is also prohibited from migrating.



12 13 14 15



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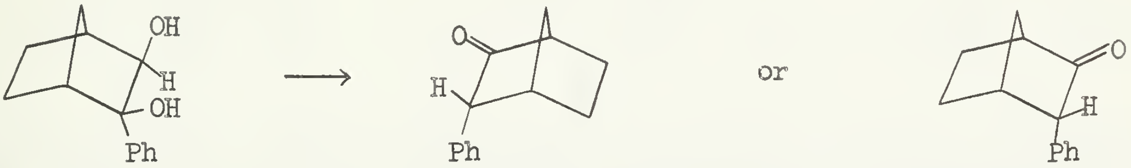
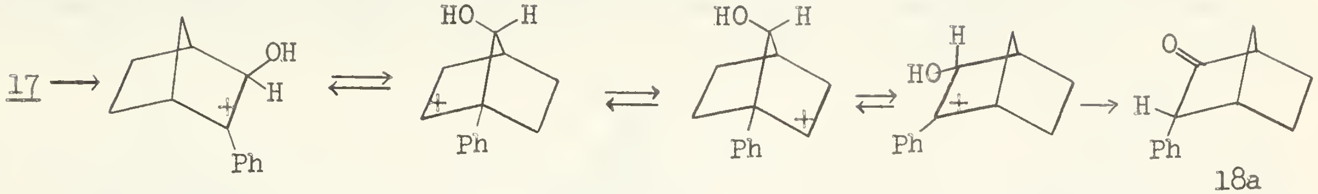
PINACOL REARRANGEMENT

Kleinfelter and coworkers[17] noted that 2-phenylnorbornane-2,3-cis-exo-diol 17 upon being heated with dilute aqueous dioxane-sulfuric acid mixture yielded 3-endo-phenyl-2-norbornanone 18. The stereochemical relationship of reactant and product was not specified. The fact that phenyl is endo in 18 precludes a simple loss of tertiary hydroxyl followed by a 3,2-endo shift of hydrogen during the rearrangement. Collins et al.[18] studied the pinacol rearrangement of compound 17 using labeling and determined that the reaction did not proceed by means of phenyl group migration or vinyl dehydration pathways, they also studied the stereochemistry of the reaction and from these experiments they came to the conclusion that the pinacol rearrangement of 17 proceeds with intramolecular migration of hydrogen from C_3 to C_2; the configuration of the ketone 18 produced is inverted with respect to the configuration of 17, and phenyl remains attached to the same carbon atom throughout the rearrange-



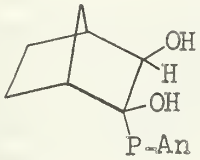
17 18a 18b

ment. One mechanism which can be written for these results is as follows.[18,19]



18a

Kleinfelter and coworkers[19] have prepared 2-p-anisylnorbornane-2,3-cis-exo-diol 19 and have carried out its rearrangement in conc. sulfuric acid at 0°C. While some sulfonation did take place, the only nonacidic compound isolable was 3-endo-p-anisyl-2-norbornanone 20 in ca. 50% yield.



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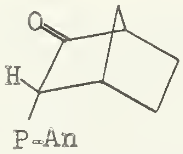

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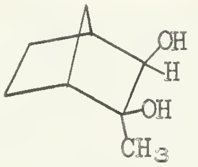

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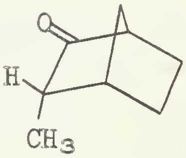

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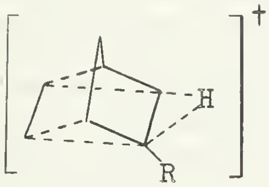
Berson and coworkers[7] provided an additional example; 3-endo-methyl-cis,exo-2,3-norbornanediol 21 rearranges in aqueous sulfuric acid to give exclusively 3-endo-methyl-2-norbornanone 22. Although no evidence was presented to show that the reaction follows the same route as demonstrated for the phenyl case, adoption of such an assumption implies that the exo-exo shift is preferred over the endo-endo shift by a factor of at least 3300.

Vicinal alkyl shifts in norbornyl systems are also observed in some other reactions.[20-24]

MECHANISTIC EXPLANATIONS

All the experimental results obtained so far demonstrate exclusively the exo-exo 3,2 shift. The traditional explanation for this stereospecificity has involved the bridged ion postulate.[1,3,6,7,12-18,25] It is argued that, since a nonclassical norbornyl cation is attacked by external nucleophiles from the exo direction, internal 3,2 rearrangements of the same ion should also favor exo migration strongly. Strictly speaking,[26] this means that the extent of charge delocalization in the transition state for exo,exo 3,2 shifts 23 must be greater than in the endo,endo transition state 25. If the two transition states were to be best described by 24 and 25, then there would be no apparent electronic reason favoring one over the other. In this case, whether or not the 2-norbornyl cation were bridged would have no relevance to the problem of the 3,2 shift.



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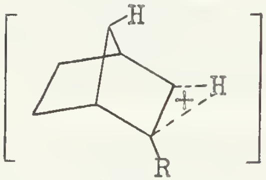

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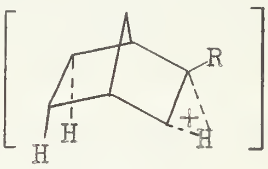

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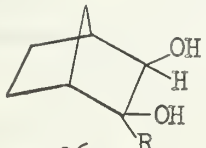
Schleyer[26] argues that the nonclassical carbonium ion theory fails to predict some of the experimental results. For instance, in the pinacol rearrangement cases, as the R in 26 is made progressively more capable of stabilizing a carbonium ion, the transition state should become less bridged and progressively more exo ketone (by 3,2-endo hydride shift) should be produced.[18,27] Yet, even with R = p-anisyl, only endo ketone was observed.[19]



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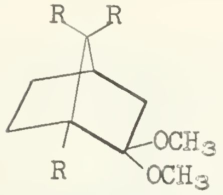
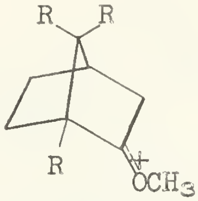
Traylor and Perrin[28] studied the mechanism of methoxyl exchange in camphor and norcamphor dimethyl ketals, 27a and

27b respectively, in methanol-d$_4$. The reaction proceeds through the classical 2-methoxybicyclo[2,2,1]heptyl-2-cation 28. They observed exo/endo rate ratios of 0.1 for camphor dimethyl ketal 27a and 16 for norcamphor dimethyl ketal 27b. Brown and



27 a,R=CH$_3$
b,R=H



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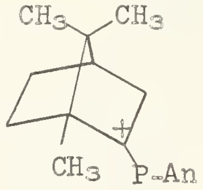
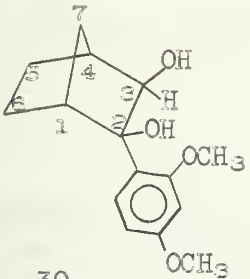


29

Bell[29] carried out the solvolysis of 29 in the presence of sodium borohydride and found that the exo/endo product ratio is 6.7. It seems that even p-anisyl is not capable of stabilizing the open carbonium ion 29. Although the transition state in the pinacol rearrangement for 26 may be less bridged for R=p-anisyl than R=CH$_3$, it may still be enough to account for the stereospecificity of the exo hydride shift.

Roberts[18] has suggested the possibility for endo migration of the C$_3$ hydrogen during rearrangement of the glycol 30, for it is conceivable that the two methoxyl groups at position 2 and 4 (on the phenyl ring) could stabilize the tertiary classical, open carbonium ion at the expense of the bridged ion.



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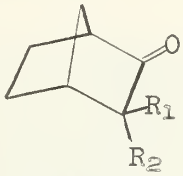
There appear to be grave difficulties with Brown's alternative explanation.[27] The exo side of the norbornane molecule is known to be less crowded than the endo toward attack by external reagent; therefore 3,2 shifts should preferentially occur exo.

However, examination of models of the two presumed transition states, 24 and 25, fails to give much support for this steric suggestion. During a 3,2-exo,exo shift 24 the migrating group must pass by the syn-7-hydrogen. In the transition states for a 3,2-endo,endo shift 25 the migrating group is favorably situated between the two normally hindering endo protons on C$_5$ and C$_6$.[26] In addition, when the migrating group is only a small hydrogen atom, the nonbonded distances would appear to be sufficiently large (>2.2 A) that no crowding should be present. Furthermore, the R group in 25 is quasi-exo, which should be favorable, while in 24 the R group is quasi-endo, more strained situation. Not only is it not clear which transition state should be of lower energy due to nonbonded steric effects, but even more seriously it would not appear possible that the energy differences between 24 and 25 could be very large. There appears to be at least a 100-fold preference for exo-exo over endo-endo 3,2 shift. One cannot explain such a 3 Kcal/mole phenomenon by an effect likely to be of much smaller magnitude.

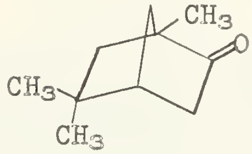
Recently Schleyer[26,30] proposed the torsional strain effect to explain this stereospecificity. Molecular models of the presumed 3,2 shift transition states 24 and 25 reveal that the arrangements around bonds C$_1$-C$_2$ and C$_3$-C$_4$ of the exo isomer 24 are nearly ideally skewed, but in the endo conformation 25 the arrangements around the same bonds are almost exactly eclipsed, an energetically unfavorable situation. Since a three membered ring has little effect in reducing the usual 3 Kcal/mole C-C rotation barrier (propylene oxide 2.56 Kcal/mole), this means that the endo transition state 25 should be less stable than the exo arrangement 24 by up to 6 Kcal/mole, this can account for the stereospecificity of 3,2 shifts without recourse either to bridging or nonbonded steric effect. The different cations-secondary, and methyl, phenyl and anisyl substituted tertiary-all of which rearrange by stereospecific 3,2 hydride or methyl shifts, have at least one unifying feature: the contrasting torsional arrangements in the isomeric situation as in 24 and 25.

Torsional theory[30] also supplies an attractive explanation for the stereospecificity of the enolization of the 2-norbornanone system. Corey and coworkers[31] carried out the methylation of 31a and showed the presence of 97% of the exo isomer 31b and at most 3% of the endo isomer 31c. 2-Norbornanone 31a,[32] isofenchone 32[32]

and camphor 33[32] exchange the 3-exo hydrogens for deuterium more rapidly than the 3-endo hydrogen. The estimated minimum exo/endo rate ratio is about 9. Since the



31 a, $R_1=R_2=H$
b, $R_1=CH_3$ $R_2=H$
c, $R_1=H$ $R_2=CH_3$



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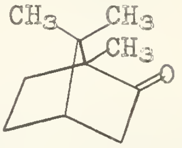

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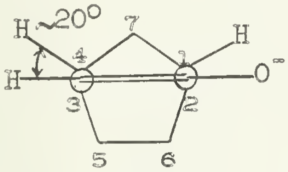
reaction site, the 3-position, is hindered by methyl from the endo side in 32 and from the exo side in 33, a steric explanation hardly seems likely. Structure 34 shows a 2-norbornanone enolate ion seen from the side, a view which emphasizes the approximate 20° dihedral angle between the bonds to the 4 and to the 3 substituent.



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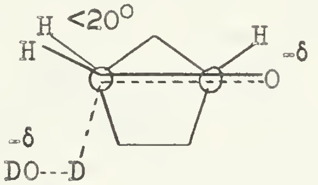

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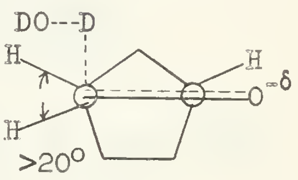

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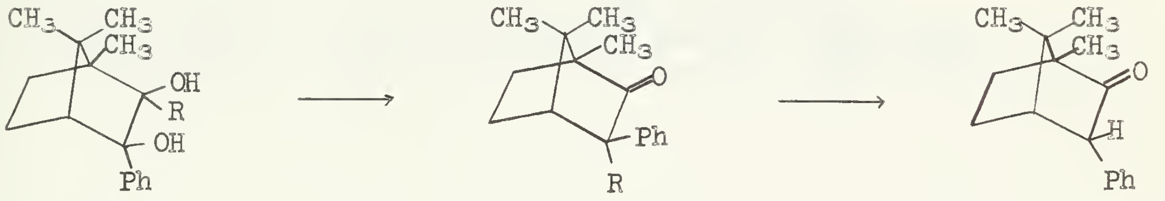
Deuteration from the exo side should be favorable, since in the transition state 36 the 3 substituent is bent toward the endo side, the dihedral angle is increased, and the torsional strain is relieved. In the transition state for endo-deuteration 35 the 3 substituent is bent toward the exo side, the dihedral angle is decreased, and torsional strain increases. Torsional strain thus favors exo over endo attack, and by microscopic reversibility, exo over endo departure.

Recently Bushell and Wilder[33] reported having treated 3-endo-phenyl-2,3-exo-cis-bornanediol 37a with 1:100 $HClO_4$-HOAc for 4 hr at room temperature; they obtained in approximately 80% yield 3-exo-phenyl camphor 38a, which undergoes slow epimerization to the endo ketone 39. Both ketones were identified by elemental analysis and



37 a, R=H
b, R=D

38 a, R=H
b, R=D

39

nmr spectra. Ketone 38a has a one proton singlet at 3.22 ppm as well as three methyl singlets at 0.59, 0.92 and 0.95 ppm. The signal at 0.59 ppm has been assigned to the syn-7-methyl which is shielded by the exo-phenyl group. Ketone 39 has a one proton doublet ($J_{3,4}$ = 4.5 cps) at 3.79 ppm, the methyl at 0.59 ppm having merged with the other methyl signal at ca. 1.0 ppm. Deuterated diol 37b was subjected to the same condition and ketone 38b was formed. Its nmr spectra in deuteriochloroform was identical with the protonated form except for the signal at 3.22 ppm. These observations represent the first case of an endo-endo migration in bicyclo[2,2,1]-heptyl series.

SUMMARY

In the 2-norbornyl cation systems, the 3,2 shift which is seen is exo-exo in all reported cases except one.[33] It is possible to explain the data either on the

basis of nonclassical carbonium ion intermediates, or, with the inclusion of torsional strain effects, on the basis of open carbonium ion intermediates. More work needs to be done, in order to have a better understanding of the mechanism.

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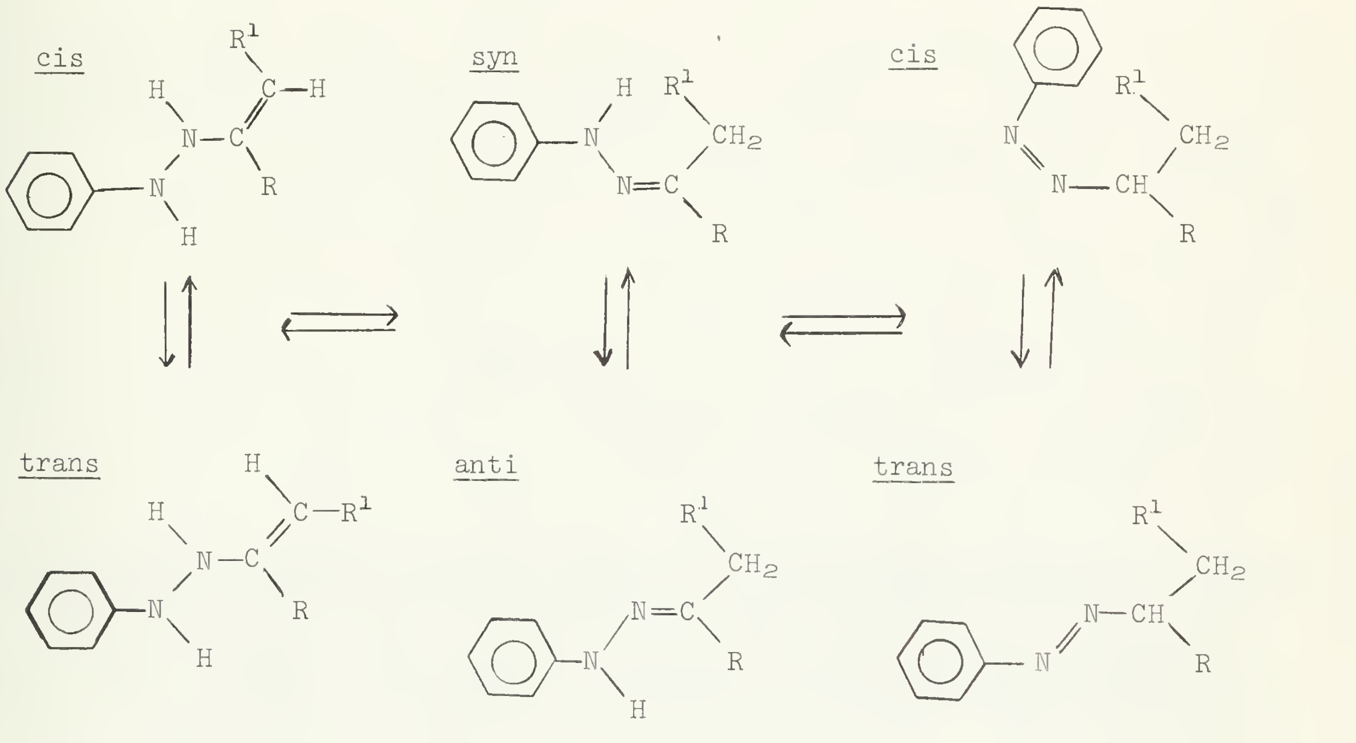
RECENT STUDIES OF PHENYLHYDRAZONE TAUTOMERS

Reported by Daniel B. Pendergrass January 11, 1968

INTRODUCTION

Arylhydrazones, particularly phenylhydrazones, have been the subject of many investigations in the last 75 years. Since Freer[1] first postulated the existence of hydrazone tautomers to explain the yellow color which developed in hydrazone solutions, their presence in polar and nonpolar media has remained a matter of controversy until the present. Many investigators have examined the problem repeatedly, and the literature contains several instances of workers who have had occasion to reverse their opinions. O'Connor[2] has provided a statement of the history of the problem.

In addition to the interest generated by the widespread use of arylhydrazones as derivatives of carbonyl compounds, the possible stereoisomers of the tautomeric forms are worthy of study.



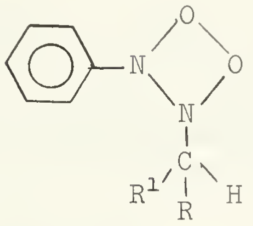
Ene hydrazine Hydrazone Azo

In the absence of resonance contributions, one can calculate from bond dissociation energies that the hydrazone form is favored over the azo and ene hydrazine tautomers by 9 and 16 kcal/mole respectively. However, MO-LCAO calculations by Arbuzov and co-workers indicate that the ene hydrazine form may be resonance stabilized to the extent of 2β by π-p-p-π interaction.[3] The I.R. spectra of phenylhydrazones typically exhibit noticeable shifts of the C=N frequency which are indicative of π-p-π interactions. The magnitude of this interaction has not been reported. Methylphenylhydrazones do not possess this type of conjugation.[4,5,6] Thus it is difficult to predict in advance which of the proposed tautomers should be the most stable.

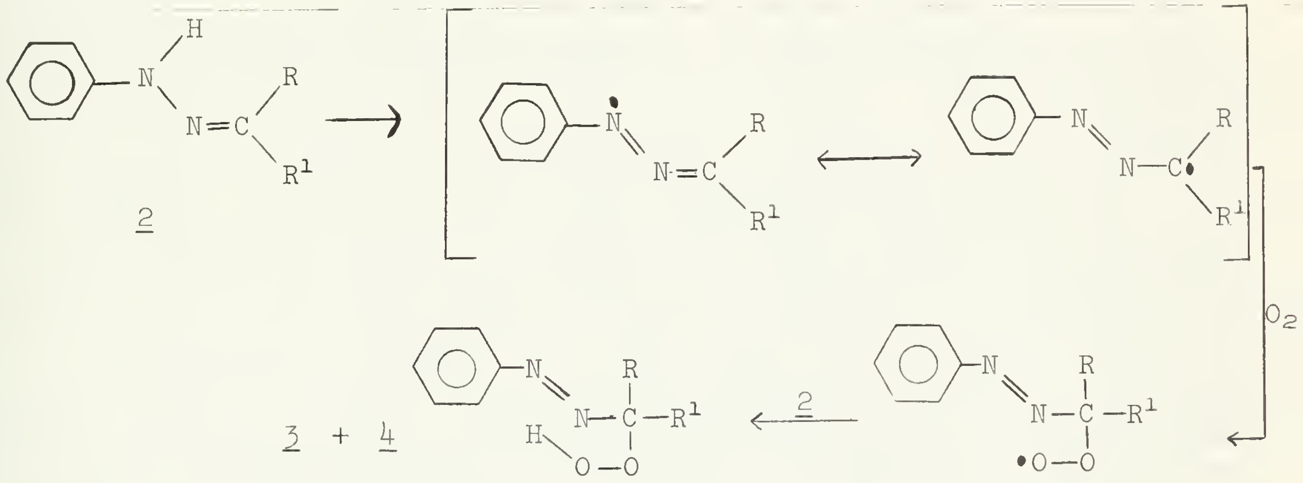
As suggested above, the existence of the ene hydrazine and azo tautomers of phenylhydrazones was postulated to explain the fact that freshly prepared solutions of phenylhydrazones are nearly colorless, but they turn yellow on standing. The observed yellow color is typical of the azo group. Many workers have carefully overlooked the implications of the work of Stobbe and Nowak[7], who reported that the yellow color did not appear in solutions which were protected by carbon dioxide.

They suggested that the coloration could be attributed to oxidation products. Busch and Dietz[8] confirmed the fact that the appearance of the yellow color was accompanied by the uptake of one mole of oxygen and proposed a cyclic structure (1) for the oxidation product.

1



In 1951, Criegee and Lohaus also found that one mole of oxygen reacted with phenylhydrazones under free radical conditions.[9] By analogy to other oxidation products[10,11] of phenylhydrazones, structure 4 was suggested. The following mechanism was proposed:



Structure 4 is consistent with spectral data now available. Spectra of these hydroperoxyphenylazoalkanes have been reported by several workers.[12-14] The N-H band of the parent hydrazones, usually found between 3100 - 3400 cm^{-1}, disappears when the solution is exposed to air. At the same time bands not found in the parent compound begin to appear. For example, exposure of cyclohexanonephenylhydrazone to air causes the appearance of bands at 1450 cm^{-1} (N=N), 1050 cm^{-1} (C-O), and 3480 cm^{-1} (O-H).[14] Other bands have also been observed by some workers. Exposure of known samples of the azo tautomer to bubbling oxygen does not give the oxidation product. This observation supports the above mechanism and seems to rule out the conversion of the hydrazone to the azo tautomer prior to oxidation.[12] The ultraviolet spectra of the hydroperoxyphenylhydrazones have maxima occuring at 266.5-268.5 mμ and 409-413 mμ (ϵ = 9,150-10,400 and 124-140 respectively.) This compares favorably with the azo tautomers whose maxima occur in the region 259.5-262.5 mμ and 405-413 mμ confirming the azo structure of the oxidation product. The n.m.r. spectra of these compounds are also consistent with the azo structure (4).[12,15]

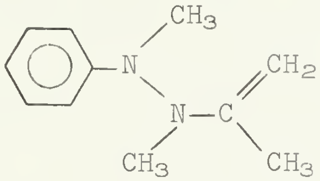
The autoxidation mechanism is supported by the fact that methylphenylhydrazones do not react. Additional support was provided by Pausaker[16], who examined the effect of substituents on the rates of oxidation of benzaldehydephenylhydrazone. Electron donors in the para-position of the hydrazine phenyl group accelerated the reaction by a factor of approximately 2. Substituents on the aldehydic phenyl group produced the opposite effect to the same degree. This study was not carefully done, but the trend of the data is sufficiently clear to argue against the formation of the azo tautomer prior to oxidation. Methylphenylhydrazones, which can not easily lose their methyl group to form the radical intermediate, are not oxidized under these conditions.[12]

Recently, a number of workers have tried to examine the question of the existence of tautomers of phenylhydrazones in solution. Unfortunately, most of them were not aware of the possibility of autoxidation or chose to ignore it. This has lead to a large number of reports of the conversion of hydrazones to the corresponding azo tautomers. In fact, most, if not all, of these reports are in error. The hydroperoxyphenylazo derivatives of simple aldehydes and ketones have spectral characteristics which are very similar to those which would be expected for the azo tautomer. Unless precautions are taken to prevent contact with the air, autoxidation products are readily formed. When such precautions are taken, phenylhydrazone solutions have been shown to be stable for up to a month with no change in their spectra.[14]

EXAMINATION OF SOLUTIONS FOR TAUTOMERS

Keeping in mind that many of the recent investigations of the behavior of phenylhydrazone solutions were not performed under conditions which would exclude the formation of oxidation products, let us examine the conclusions reached in the current literature.

Spectral studies of phenylhydrazone tautomerism share a common problem, that of the selection of appropriate model compounds. If phenylhydrazones are used as models of themselves, the presence of tautomers in solution may render the information thus obtained useless for the investigation of other systems. Methylphenylhydrazones have often been used as models for phenylhydrazones, but the observed disruption of the π-p-π conjugated system[4,5,6] which the methyl group introduces would be expected to produce changes in the spectra which might prevent identification of small quantities of tautomers. Unless the methylphenylhydrazone selected has no hydrogens on the carbons α to the carbon-nitrogen double bond, the ene hydrazine tautomer may be present. If it is, this will further obscure the question of the expected position of the C=N absorption. The position of the C=N bond (and the C=C bond of the ene hydrazine if it is present) absorption is usually under a portion of the phenyl group absorption at 1600 cm^{-1}. Kitaev[5] has observed shoulders in this region which change with time for the phenylhydrazones of acetone and methylethylketone. His experimental conditions and incomplete description of the spectra do not allow this small change to be assigned to the presence of tautomers in solution. The uncertainty of assignments made on the basis of absorptions in the 1600-1645 cm^{-1} region may be emphasized by the fact that the best model for the ene hydrazine tautomer, 1,2-dimethyl-2-isopropenyl-1-phenylhydrazine, (5) has its C=C absorption[6] at 1645 cm^{-1}. This is the same position at which the C=N absorption of methylphenylhydrazones is commonly found.[2,4,6] Conjugation of the p electrons on nitrogen in compounds without the 1-methyl would shift both the C=C and the C=N bands toward the phenyl band at 1600 cm^{-1}.



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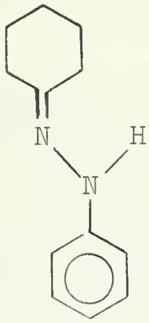
The use of azobenzene as a model for the azo tautomer has been criticized by O'Connor[2] because of the extensive conjugation expected between the two phenyl groups and the nonbonding electrons on nitrogen. Subsequent investigation of a number of phenylazoalkanes has shown that delocalization is extensive in all cases. The spectra of known phenylazoalkanes remained constant with time.[2] Exposure of solutions of phenylazoalkanes to sunlight or fluorescent lighting does produce changes in the observed spectra which may be attributed to the *cis-trans* isomerization of the azo group.

Examination of a number of phenylhydrazones in nonpolar solvents leads to the conclusion that only the hydrazone form is present in freshly prepared solutions which have been protected from oxygen.

Karabatsos and co-workers, in a series of papers,[17-22] have studied the conformational and configurational isomers of a series of phenylhydrazones by n.m.r. During the course of these studies, no detectable quantaties of an ene hydrazine or azo tautomer were observed. On the basis of chemical shifts, syn and anti configurations may be assigned. Phenylhydrazones of aldehydes exist in the anti form. The derivatives of ketones are found in both the syn and anti forms. The relative amounts of the syn and anti isomers appear to depend on the bulk of the substituents rather than their inductive effects. Solvent and dilution studies indicate that hydrogen bonding of phenylhydrazones to solvents such as benzene may affect the chemical shifts of protons cis or trans to the anilino group to different extents confirming previous conformational assignments.

CYCLOHEXANONEPHENYLHYDRAZONE

During the last 10 years, cyclohexanonephenylhydrazone (6) has been discussed by many of the workers mentioned earlier because it apparently exhibits anomolous behavior. O'Connor[2] reported that 6 is converted in good yield to the azo tautomer (7). The conversion was followed by ultraviolet spectroscopy and by n.m.r.. In dilute solutions in hexane the reaction was nearly complete in 7-10 minutes. The reaction was slower in CCl_4 and in methanol.



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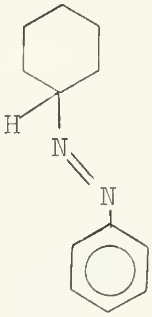

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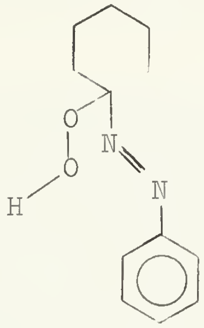

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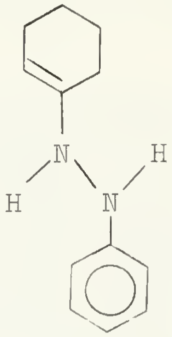

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Kitaev[4] examined a series of phenylhydrazones of aldehydes and ketones and reported analogous results. Neither investigation reported precautions against autoxidation to the hydroperoxyphenylhydrazone 8. This oversight was quickly pointed out by Bellamy and Guthrie[13], who observed no changes in the spectra of suitably protected solutions of phenylhydrazones. It was also noted that the spectra of the authentic azo compounds differed slightly from that of the corresponding phenylhydrazone solution through which air had been bubbled. Kitaev[14] quickly agreed. Bellamy then strengthened his position by comparing the n.m.r. spectrum of the azo tautomer to that of the hydroperoxyphenylazo compound 8 produced by bubbling oxygen through a solution of 6 in benzene-d 6. They were not the same. This lead O'Connor to repeat his previous work.[25] Oxygen free solutions of 6 in nonpolar solvents remained unchanged. Solutions saturated with oxygen gave only the autoxidation product 8. However, freshly distilled solvents which were not protected from the air converted the hydrazone 6 to the azo tautomer 7 in a few minutes. This lead O'Connor to suggest that the presence of trace amounts of oxygen may serve to catalyze the conversion of hydrazones to the more stable azo tautomers, while in the presence of excess oxygen the hydroperoxyphenylazo compounds are formed. This hypothesis has recently been modified by Kitaev[26], who has observed the formation of 8 prior to the formation of 7. He also reports that solutions of hydroperoxyphenylazoalkanes decompose on standing to the corresponding azo compounds. Throughout the above studies no ene hydrazine was detected. This does not exclude the presence of tautomers such as 9 in polar solvents. Polarographic studies[25,6] of phenylhydrazones in buffered methanol solutions indicate that the azo tautomer is the most stable form in the pH range 5.8 to 9.2. This is in agreement with equilibration studies using

the dimethylhydrazones of ketones.[26,27] Ring strain may be a factor in the unusual reactivity of 6[27] However attempted equilibration of 6 and 7 under radical conditions seems to indicate that the hydrazone is the more stable form. After 24 hours at 100°, a solution of cyclohexanonephenylhydrazone with a trace amount of benzoyl peroxide contained only starting material. In a similar experiment, 7 was converted to 6 in 54% yield when the solvent was CCl_4. Eleven percent of the starting material was recovered The yield of 6 was higher in hexane. Similar azo to hydrazone conversions have been accomplished in the presence of acids and bases.[28] This indicates that the hydrazone is thermodynamically more stable than the azo tautomer

HYDROGEN EXCHANGE

In very recent hydrogen exchange experiments, Simon and Moldenhaur[29] report that the phenylhydrazones of simple aldehydes and ketones do not exchange the carbon bonded hydrogen in neutral ethanol solutions This indicates that the tautomeric forms are not interconverted in solution with the azo and ene hydrazines present in low concentrations. In ethanolic KOH, aldehyde derivatives exchange both the aldehydic proton and the hydrogens of the α carbon. Para-substituted benzaldehyde phenylhydrazones exhibit exchange rates consistent with the Hammet equation. Substituents in the aldehyde portion of the molecule enhance the rate of exchange while those in the hydrazine portion retard the exchange to a similar extent.

SUMMARY

In nonpolar solvents, freshly prepared solutions of phenylhydrazones are the hydrazo tautomer. If air is not excluded, phenylhydrazone solutions may be converted to peroxyphenylazo compounds which then decompose to the corresponding phenylazo compounds. The results of equilibration studies of hydrazones and azo compounds are contradictory. Both the azo and hydrazo tautomers have been shown to be the most stable. Polarographic studies have shown that varying the degree of buffering changes the observed tautomers. In nonbuffered or alkaline methanolic solutions only the azo tautomer is observed polarographically.[30] Hydrogen exchange studies indicate that no exchange occurs in neutral ethanolic solutions. This indicates that no tautomerization is occuring. The ene hydrazine has been observed only be polarography. Bromination does not occur through the ene hydrazine, since optical activity is retained at the α carbon. Phenylhydrazones which can not form the ene hydrazine tautomer are brominated at the same rate as those that can.

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